THE BEHAVIOURAL EFFECTS OF ANDROGENS IN MEN

by

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PUBLICATIONS RELATED TO THE STUDIES DESCRIBED

O'CARROLL, R.E. (1983). Plasma steroids and sex hormone binding globulin estimation. Clinica Chimica Act (In Press).

BANCROFT, J., O'CARROLL, R.E., McNEILLY, A. & SHAW, R. (1983). The effects of bromocriptine on the sexual behaviour of a hyperprolactinaemic man: a controlled case study. International Journal of Andrology (In Press).

O'CARROLL, R.E. & BANCROFT, J. (1983). Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. British Journal of Psychiatry (Submitted).

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Declaration of the author's participation in the work submitted

The composition of this thesis is that of the author, who was assisted in the design of the studies by Dr. J. Bancroft.

No part of this work has been accepted, or is being submitted for any other degree.

The author was responsible for the organisation of the research, recruitment of the subjects, carrying out the psychometric testing and structured interviews, collecting the blood samples, performing radioimmunoassay on these samples for testosterone, DHT and sex hormone binding globulin (SHBG), carrying out the nocturnal erection measurements and analysis of the data.

Chromatographic separation of DHT from competing steroids was performed by Mr. D. Davidson. Radioimmunoassay of LH, FSH and prolactin was performed by Miss H. Ainslie and "free" plasma testosterone estimation was carried out by Dr. E. Bergink. Intramuscular injections of testosterone and placebo were administered to the subjects by Sisters J. Gray and A. Cook.

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ABSTRACT

A series of studies are presented which attempt to answer specific questions concerning the androgen-behaviour relationship in the adult human male.

A critical review of the literature revealed that the androgen-behaviour relationship in the human male has been poorly researched. In particular, unsatisfactory experimental methodology and inexact operational definitions of behaviour have been employed. In the studies presented in this thesis an attempt was made to specifically define dysfunctional states and to carefully monitor the resultant behavioural effects of androgen administration.

In the hypogonadal man, a dose-dependent relationship was demonstrated for specific aspects of sexual functioning, in particular self-rated interest in sex and frequency of morning erections appeared to vary with androgen replacement dose.

In the eugonadal man, intramuscular depot injections of testosterone were shown to be the best method of overcoming the homeostatic mechanisms and increasing circulating androgen levels in the blood.

High dosage testosterone administration acted to increase the level of sexual interest of a group of men whose presenting complaint was loss of libido. This treatment, however, did not result in an increased frequency of sexual activity. High dosage testosterone administration had no behavioural effect, compared with placebo, in a group of eugonadal men presenting with erectile dysfunction.

Androgen administration appeared to have a stimulatory effect on the nocturnal erections of a group of hypogonadal men, although

androgen withdrawal resulted in differing rates of diminution of nocturnal erectile response. In contrast, androgen administration had no effect on the nocturnal erections of a group of eugonadal men presenting with erectile dysfunction.

Androgen administration to hypogonadal and eugonadal men had a general lack of effect on a series of psychometric test scores, which measure various aspects of cognitive functioning and personality. (Previous investigators had proposed that these test scores were correlated with circulating androgen levels).

A case study is presented, reporting the lack of behavioural effect of oral testosterone undecanoate administration in an institutionalised hypogonadal man who had previously responded very aggressively to testosterone injections.

The implications of these experimental findings are discussed in relation to the results of previous studies.

CHAPTER 1

GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1 HISTORICAL INTRODUCTION

For centuries, the products of the testes have been thought to play an important functional role in the genesis and maintenance of behavioural masculinity. Radical reduction of circulating androgen levels, i.e. castration, has been carried out on man and animals since pre-historic times (Medvei, 1982). However, to this day, the exact behavioural effects of circulating androgens in man remains to a large extent a mystery.

Animal evidence (see reviews by Davidson, 1972; Davidson and Levine, 1972) suggest that androgens are necessary at critical periods in development in order to organise the central nervous system in a manner conducive to later adult male behaviour, which is in turn dependent on circulating androgen levels in adulthood. The exact behavioural functions of circulating androgens in adult men, however, have yet to be elucidated. Historically, behavioural observations have been confined largely to the effects of castration.

Castration of male animals has been carried out for four main reasons:-

(a) for gastronomic purposes, as gelded animals tend to put on fat and give a more tender meat (Needham & Gwei-Djen, 1968)

(b) to induce sterility

(c) to curb aggression, e.g. in the horse

(d) in order to use the testicular tissue for pharmaceutical preparations (see below).

The behavioural effects of this operation, principally diminished sexual behaviour and increased passivitiy, have been known to students

of animal husbandry since described by Aristotle (384-322 BC).

Men have been castrated for a variety of medical and social reasons:-

(a) as a form of punishment for criminals (Heim and Hursch, 1979)

(b) as a form of psychiatric treatment with the aim of reducing aggressiveness or deviant sexual behaviour, e.g. as recently as this century, castration was claimed to be effective in the "treatment" of masturbation in adolescent boys (Flood, 1901)

(c) as a means of ensuring lack of potency, e.g. the eunuchoid guardians of the harem in ancient Rome and Egypt

(d) as a form of surgical therapy, e.g., in the treatment of testicular carcinoma

(e) as a means of preventing development of the secondary sex characteristics, e.g. the castrati singers of 18th and 19th century Italy.

The loss of sexual potency often displayed by castrated men led Susruta as long ago as 1400 BC to recommend the eating of animal testicular tissue as a treatment for sexual impotence (Newarla, 1943). Pliny the Elder made the same recommendation, though much later in time (23-79 AD) and Mesuë the Elder (777-837 AD) prescribed testicles as an aphrodisiac (both cited in Medvei, 1982). Surprisingly it was not until 1132 AD that Hsu Shu-Wei proposed the use of testicular extracts as replacement therapy for male hypogonadism (Needham and Gwei-Djen, 1968). These testicular preparations were unlikely to have had any more than a placebo effect, principally because the oral route leads to inactivation of the bio-active testicular products (principally

testosterone) by the liver. However, Needham and Gwei-Djen (1968) suggested that the administration of animal testicular tissue by the mouth, if in significant quantity, could have had reasonably significant effects. This is extremely unlikely, as Nieschlag and Freischem (1982) have calculated that approximately 3 kg of animal testes would have to be consumed in order to equal the daily testosterone production of a normal adult male; even then the steroid would be completely and rapidly inactivated in the liver.

As Newarla (1943) points out, from the middle ages until the turn of the century, little progress was made in our understanding of the behavioural effects of androgens in man. This field of research, however, received much attention in 1889 when Brown-Sēquard published his famous and controversial work on the effects of self-administered injections of testicular extract. He claimed, at the age of seventy-two, an improvement in general health, muscular strength and appetite, as well as improvement in his mental facilities. Unfortunately, this uncontrolled study, together with subsequent extravagant claims for the rejuvenative effects of testicular extract injections led many to try Brown-Sēquard's treatment. As this "therapy" was almost certainly useless, this led to many seekers of perpetual youth being extremely dissapointed with the results. In reviewing the effects of the Brown-Sēquard (1889) study, Newarla (1943) states "The susceptibility of many minds in matters pertaining to sex and the false hopes raised by extravagant claims led inevitably in a pendulum fashion to a viewpoint strongly antagonistic to the acceptance of the efficacy of any testicular substances".

This negative attitude, reinforced by the lack of therapeutic success reported for testosterone treatment in men complaining of erectile impotence (see section 1.4) has persisted over the last century and has resulted in a lack of properly controlled experiments designed to investigate the role androgens play in the regulation and expression of behaviour in the adult human male. To quote Davidson and Levine (1972) "One cannot fail to note in current and past literature the impressive dearth of definitive studies on the endocrinology of human sexual behaviour. In this vacuum, inadequate clinical impressions and pseudodata often masquerade as well established phenomena. There is a great need for large scale investigations of endocrine-sexual behaviour relationships in human males and females using acceptably objective behavioural criteria and the appropriate controls".

Some progress has been made in the last decade to fill the gap indicated by Davidson and Levine (1972), but it is fair to say that the precise relationships between androgens and behaviour in man are still unknown. In this thesis an attempt is made to address some of the outstanding questions.

1.2 ANDROGEN-BEHAVIOUR RELATIONSHIPS TO BE INVESTIGATED

As will become apparent in the review of the literature that follows (1.3-1.8), there are many hypothesised relationships between androgens and behaviour in men. It was therefore necessary to select out what were, in the author's opinion, the most theoretically important and promising topics for investigation. In general, the approach taken by the author has been an experimental rather than a

correlational one, in that behavioural response to endocrine manipulation in the hypogonadal and eugonadal man has been studied. In particular, the studies have focused on the effect (or lack of effect) of androgen administration on sexual behaviour (i.e. sexual activity, sexual interest and erectile function), mood state, personality and cognitive functioning.

The specific questions which the author has attempted to answer in this thesis are:-

(1) Is there a relationship between androgen replacement dose and behavioural response in the hypogonadal man, and what aspects of behaviour are affected by androgen replacement? (Chapter 3)

(2) In the eugonadal man, what is the best method of overcoming the gonadal steroid homeostatic control mechanisms in order to raise circulating androgen levels so that behavioural responses to endocrine manipulation can be studied? (Chapter 4)

(3) Is high dosage testosterone administration an effective form of treatment for eugonadal men complaining of reduced sexual interest? (Chapter 5)

(4) Is high dosage testosterone administration an effective form of treatment for eugonadal men complaining of erectile dysfunction? (Chapter 6)

(5) Does androgen administration have an effect on nocturnal erectile function in hypogonadal and eugonadal men? (Chapter 7)

(6) Does androgen administration have an effect on personality measures and cognitive functioning in hypogonadal and eugonadal men? (Chapter 8)

(7) Does androgen administration have an effect on aggressive behaviour in man? (Chapter 9)

LITERATURE REVIEW

1.3 HYPOGONADISM IN THE MALE-BEHAVIOURAL EFFECTS OF ANDROGEN REPLACEMENT

Hypogonadism in the male (i.e. a marked reduction or absence of normal levels of circulating androgens) is a well documented clinical phenomenon (Nieschlag and Freischem, 1982). Uncontrolled clinical reports have suggested that the most common behavioural consequences of male hypogonadism are a reduction in the level of sexual interest, an increased incidence of erectile difficulties and a marked reduction in the frequency of overt sexual activity, all of which can be improved following androgen replacement therapy (Whitelaw, 1958; Beumont et al., 1972; Franchimont et al., 1978; Maisey et al., 1981).

Surprisingly, it is only in the last four years that methodologically acceptable studies have been carried out which have conclusively demonstrated that exogenous androgen administration is superior to placebo with respect to beneficial effects on the sexual behaviour of the hypogonadal man (Davidson et al., 1979; Skakkebaek et al., 1981).

1.3.1 Androgen Effects on Sexuality-Behavioural Mechanism of Action

"No clinician or researcher who has observed a hypogonadal patient begin his transformation from a eunuchoid state to renewed sexuality at the touch of a needle containing testosterone can fail to experience considerable wonder over how the hormone works" (Davidson et al., 1982).

To date, there have been three major hypotheses presented concerning the mechanisms underlying the behavioural effect of androgen replacement in hypogonadal men.

1.3.1.1 Androgens Act Primarily on General Metabolism and Mood?

Kinsey and his colleagues proposed (without supplying supportive evidence) that androgens act primarily to enhance general metabolism and mood in a relatively non-specific way, and hence influence sexuality, among other behaviours, as part of a general activational effect (Kinsey et al., 1953). Evidence to test the Kinsey hypothesis dervived from hypogonadal studies is conflicting. While Davidson et al. (1979) and Salmimies et al. (1982) reported a lack of effect of testosterone replacement on mood, Luisi and Franchi (1980) claimed that "mental state" (as assessed using an unpublished mood questionnaire) was markedly improved following androgen replacement therapy. Similarly, Skakkebaek et al. (1981) found that fatigue and tension/anxiety were reduced and vigour increased during active treatment as compared with placebo. However, in neither study did the mood change precede the androgen effect on sexual behaviour.

Data from the eugonadal man is equally conflicting. Results of longitudinal studies correlating fluctuations in endogenous testosterone level with self-rated mood state have been shown positive (Mazur and Lamb, 1980), negative (Houser, 1979), and no association (Doering et al., 1974).

1.3.1.2 Androgens Act to Enhance Mental and Sexual Imagery?

In attempting to account for the fascinating finding that the ability to produce erections in response to erotic film appears to be relatively independent of androgen status (Bancroft et al., 1974) whereas the ability to produce erections in response to sexual fantasy does appear to be dependent on an adequate androgen level in men (Bancroft & Wu, 1983), Bancroft (1980) formulated a hypothesis which suggested that one of the effects of androgen replacement may be to facilitate mental imagery in a relatively non-specific manner. Bancroft (1980) suggests that the well documented visuo-spatial superiority of the male from puberty onwards (i.e. when marked sex differences in circulating androgen levels appear, see section 1.6) lends support to his hypothesis. Also anecdotal clinical reports have been published which suggest that some hypogonadal men report a reduced incidence of erotic imagery and daydreams (Money, 1961). However, preliminary evidence suggests that androgen replacement therapy does not act to improve the spatial ability of hypogonadal men (Hier and Crowley, 1982).

Bancroft (1980) also claimed that the observation that testosterone administered to chickens acted to increase their "persistence of attention" as assessed by the length of pecking runs on preferred as opposed to non-preferred food (Andrew and Rogers, 1972) lends additional support to his hypothesis in that testosterone is acting to facilitate this active cognitive process. Equating feeding behaviour in chickens with mental imagery and sexual fantasy in the human male is a conceptual and phylogenetic leap open to criticism.

In fairness, recent evidence has suggested that androgens may act to improve performance on stereotyped repetitive tasks, e.g. serial subtraction in the human (Broverman et al., 1980) but it must be stated that this simple repetitive type of task appears far removed from the cognitive sophistication required for the generation and maintenance of visual imagery and sexual fantasy in man.

1.3.1.3 Androgens Act to Increase the Pleasurable Awareness of Sexual Response?

The most recent hypothesis which attempts to explain the behavioural mechanism of action of androgens in man was proposed by Davidson et al. (1982). These authors suggest that androgens may act to facilitate sensitivity to, or pleasurable awareness of, both sexual thoughts and actions. This intriguing hypothesis postulates that testosterone administration may act:-

(a) to increase the awareness of sexual response, presumably by reducing thresholds of genital sensitivity, and

(b) to make this increased genital awareness more pleasurable, possibly via androgen mediated effects on "pleasure centres" in the central nervous system (Olds & Milner, 1954). This hypothesis that androgens act to alter neural thresholds has recently received support from work carried out on the rat. Bermond et al. (1982) demonstrated that androgen administration acts to reduce the hypothalamic theshold at which electrical stimulation induces aggressive behaviour in the castrate male.

Davidson et al. (1982) suggest that their hypothesis could account for all the observed changes in sexual behaviour which occur during

androgen replacement and withdrawal in the hypogonadal man. They state "The behaviour-reinforcing properties of sexual pleasure could suffice to explain all effects of androgen on sexuality through a domino process involving increased sexual thoughts or fantasies, spontaneous erections (including nocturnal ones), coitus or masturbation, satisfaction and even ejaculation". As yet, supportive evidence for this hypothesis is lacking.

In this thesis an attempt is made to shed light on the validity of each of the hypotheses outlined above which claim to provide the mechanism underlying what has been described as the most phylogenetically stable, biologically important known action of a hormone on behaviour.

1.3.2 Androgen Replacement in the Hypogonadal Man - Relationship Between Dose and Behavioural Response

Dose-response relationships between testosterone replacement and sexual behaviour have been reported in the rat (Damassa et al., 1977) and in the ram (D'Occhio and Brooks, 1982). The situation in the human male is less clear. Davidson et al (1979) claimed to have demonstrated a dose-response relationship in six hypogonadal men. These authors reported that in a blind design, injections of 400 mg of testosterone enanthate consistently produced superior results as compared with 100 mg injections or with placebo injections. This evidence in support of a dose-response effect was criticised by Bancroft (1980) who pointed out that following the 100 mg injection, circulating plasma testosterone levels were maintained within the normal range for less than half of the four week behavioural assessment period, in contrast

to the four weeks following the 400 mg injection of testosterone. Bancroft argues that "in averaging the behavioural scores for the whole four-week period, the difference between the two regimens could be accounted for simply by a shorter duration of hormone effect with the lower dose rather than a true dose-response relationship". Davidson et al. (1982) answered this criticism by re-analysing the data from their 1979 paper, this time comparing the frequency of sexual events involving erection during the first two weeks following each injection. For each of the six subjects the frequency of erections was significantly higher in the two weeks following the 400 mg injection as compared with the two weeks following the 100 mg dose. Similarly there was a significantly higher frequency of erections during the 100 mg testosterone administration phase as compared with matched placebo. This evidence is suggestive of the existence of a dose-response relationship in the human male, but firm conclusions cannot be drawn from a study using only two different doses of androgen.

Recently the results of a more extensive study investigating the dose-dependent effects of testosterone replacement on the sexual behaviour of hypogonadal men were presented (Salmimies et al., 1982; Pirke & Kockott, 1982). In this single-blind study, fifteen male hypogonadal patients were administered injections of testosterone, 25 mg for the first month followed by successive one month periods on placebo, 50 mg, 100 mg and 250 mg doses of testosterone (injections were administered every two weeks throughout the study).

The authors reported that four out of the fifteen patients exhibited a marked degree of sexual activity while receiving placebo. However, when the data from the remaining eleven men was analysed, a dose-dependent relationship was observed during administration of the 50 mg, 100 mg and 250 mg dose regimes (the 25 mg injections of testosterone did not significantly affect the reported frequency of erections or ejaculations as compared with placebo). This study is open to criticism on three counts:-

(a) all the men received gradually increasing doses of testosterone, and it is possible that the subjects may have expected gradual increments in their replacement dosage and consequently their behavioural changes may have been more due to expectation, rather than because of a genuine hormone mediated effect

(b) the study was not double blind

(c) the four hypogonadal men whose behavioural response did not conform to the dose-dependent hypothesis were excluded from the analysis.

Taken together the data from the Davidson et al. (1979) and the Salmimies et al. (1982) studies are suggestive of a possible dose-response relationship existing between androgen replacement and the sexual behaviour of the hypogonadal man. However, studies utilising better experimental design, with better control over androgen dosage (e.g. oral as opposed to intra-muscular route of administration) would provide more conclusive evidence.

1.3.3 Behavioural Effects of Different Androgens

Very little research has been carried out looking at the relative behavioural efficacy of different androgens in the human male. The few studies that have been carried out have produced contrary findings.

Bancroft, Wu & Davidson (unpublished data) found rectal suppositories of DHT to be less effective than T.U. in the treatment of male hypogonadism (however the plasma levels of DHT achieved following DHT treatment were modest). Luisi and Franchi (1980) similarly reported that treatment with mesterolone, which like DHT is non-aromatizable, was without significant effect compared with testosterone undecanoate (T.U.) in a group of hypogonadal men. Gooren (1982), however, switched six hypogonadal men from their existing androgen replacement regime of T.U. 120 mg/day to DHT undecanoate 120 mg/day for twelve weeks and observed no deterioration in sexual functioning.

Further research is obviously required to clarify the relative behavioural efficacy of these different androgen preparations. As Davidson *et al.* (1982) state, "It remains important that further adequate research be done on the relationship between molecular structure and sexual function of androgens in humans,....in order to clarify the question of what molecular transformatins androgen might undergo prior to its action on sexuality".

1.4 ANDROGENS AND IMPOTENCE

1.4.1 Androgen Levels in Impotent Men

As a result of the clinical evidence suggesting that androgen deficiency is often associated with sexual dysfunction in the male, a number of studies have been carried out over the past few years evaluating the androgen status of men complaining of erectile impotence.

In one of the first studies to be published, Ismail et al. (1970) reported that the urinary excretion of testosterone metabolites was reduced in impotent men as compared with controls. With the development of accurate radioimmunoassay techniques, researchers continued the pioneering work of Ismail et al (1970) and attempted to correlate plasma androgen levels with sexual dysfunction in the male.

Legros et al. (1973) claimed that mean plasma testosterone levels were reduced in impotent men compared with normal controls. However, the authors did not specify the number of blood samples taken from each subject. This is an important methodological point, as rapid episodic fluctuations in plasma testosterone levels have been shown to occur in the normal man (Doering et al., 1974; Murray and Corker, 1973; Rowe et al, 1974).

Racey et al (1974) were the first investigators to carry out a study which controlled for this intra-individual variation in androgen levels. The authors obtained three morning and three afternoon blood samples from each subject and found that the mean testosterone level of a group of impotent men did not differ from that obtained from a normal control group. Similar negative findings were reported by

Lawrence and Swyer (1974), Ansari (1975) and Comhaire & Vermeulen (1975).

More recently Pirke et al. (1979) and Schwartz et al (1980) have carried out more detailed endocrinological investigations of men presenting with sexual dysfunction. Again, circulating testosterone levels were not significantly different when the patient group was compared with controls. However, when Schwarz et al. (1980) divided their rather heterogenous patient group into specific diagnostic categories, they found that men with primary impotence had significantly higher testosterone levels than men with secondary impotence. Pirke and Kockott (1982) failed to replicate this finding. The Schwartz et al. (1980) study can be criticised as can most of the studies in this area, in that only one blood sample was taken from each subject. Interestingly, Schwartz and his colleagues defend their sampling regime by stating "Variation in a large group due to oscillation is random and therefore tends to cancel itself out; furthermore, recent data show that single blood samples of testosterone are good estimates of the 24 hour plasma integrated concentration (Urban et al., 1979)". However, the Urban et al (1979) study deals solely with the problems associated with gonadotrophin measurement - testosterone measurement is not mentioned in the entire paper!

Three additional studies have recently been reported where the investigators determined the endocrine status of consecutive clinic presenters complaining of sexual dysfunction. In the U.S.A. Spark et al (1980) screened one hundred and five consecutive male patients presenting at an endocrine clinic complaining of erectile impotence.

Of these, thirty-seven men were found to have some degree of hypogonadism, eight were hyperprolactinaemic and two had evidence of hyperthyroidism. Nahoum (1982), working in Brazil, similarly determined the endocrinological status of two hundred and five consecutive impotent patients. Nahoum reported that seventy-two men (35.1% of the sample) were shown to have reduced testosterone levels. This figure agrees well with that of 29.7% of impotent men who were also shown to have reduced testosterone levels by Spark et al. (1980). Combining the data from these two studies, approximately one third of the impotent men investigated demonstrated signs of androgen deficiency. This is a surprisingly high proportion, (a) in light of the previous negative reports in the literature and (b) given the widely held view that 90-95% of all cases of impotence are psychological in origin. (Although as Bancroft (1982) states "where this figure came from was never clear, but it has entered into medical folklore". Spark et al. (1980) suggest that this greater than 90% estimate originated from Strauss (1950) who maintained, without providing supportive evidence that "impotence was psychic....in considerably more than 90% of the cases"). Contrary data, however, was supplied by Batrinos et al. (1981) who investigated the testosterone levels of fifty-seven consecutive Greek men presenting with impotence at an endocrine clinic. Of these, only six (10.5%) were subsequently shown to have reduced testosterone levels.

When one attempts to weigh up the evidence for and against functional androgen deficiency in men complaining of impotence, one is forced to conclude that the case remains "not proven". As Schiavi and

White (1976) point out "Methodological differences in number, frequency and time of blood samplings and inadequate matching of control groups may account for some of the discrepancies in findings". It is also of crucial importance to note that in most of the studies carried out to date, investigators have generally not provided detailed clinical information regarding their patient sample. In particular operational definitions of dysfunctional states have been lacking, all disorders being grouped together under the global term "impotence". For example, men with erectile difficulties but with a normal degree of interest in sex, and men whose primary problem is one of loss of libido have often been combined and studied as one group. Only three studies have been published which have specified loss of libido in the impotent group under investigation. Interestingly, all three provided evidence of reduced testosterone levels in such individuals when compared with normal controls or with men with erectile dysfunction who had a normal degree of interest in sex (Cooper et al., 1981; Raboch et al. 1975; Batrinos et al. 1981). The results of these studies appear to be suggestive of a possible relationship between androgen defecit and loss of sexual appetite. However, further research is necessary before any firm conclusions can be made.

1.4.2 Androgen Administration in the Treatment of Impotence

Androgens have been used extensively with varying degrees of therapeutic success in the treatment of disorders of male sexual functioning (for review, see Kilmann and Auerbach, 1979). This field of research has been particularly lacking in well controlled, methodologically sound experiments. For example, several authors have claimed testosterone administration to be beneficial in the treatment

of erectile impotence, yet have not compared the androgen with placebo. One such study was reported by Maddison (1973). The author found testosterone treatment to be behaviourally effective in the treatment of a group of men complaining of impotence, but stated that cross-over trials could not be carried out for ethical reasons. "I could not give dummy preparations to men who expected active treatment" (Maddison, 1973). With this attitude by no means uncommon, the scientific assimilation of knowledge in this area has progressed extremely slowly. To the present author's knowledge, there have been only four controlled studies published which have compared the efficacy of testosterone versus placebo in the treatment of impotence in the eugonadal man.

The first of these studies was carried out by Bruhl and Leslie (1963), who compared the efficacy of a methyltestosterone preparation against placebo in a double blind design. The authors claimed a significant drug effect; however, the clinical and endocrine details were not reported. In 1970 Jakobovitz carried out a similar study where he compared the efficacy of a combined methyltestosterone and thyroid extract preparation with matched placebo in one hundred impotent subjects. Jakobovitz claimed that a "favourable response" was noted in 78% of the men receiving the active preparation compared with 45% of those receiving placebo. This would appear to be a convincing demonstration of the efficacy of the androgen preparation over placebo. However, again the details of the study were not reported, and in light of the preparation used, it is entirely possible that the beneficial effects were due to the thyroid extract alone. In a similar study,

Cooper et al. (1973) compared a combined preparation containing methyltestosterone, strychnine and caffeine against placebo in the treatment of erectile impotence. The authors reported slight transient beneficial effects of the active preparation compared with placebo. However, the authors themselves concluded that the improvement was probably due to the central nervous system stimulation caused by the non-steroid constituents of the preparation.

From a methodological point of view, perhaps the most satisfactory study that has been published to date is that of Benkert et al. (1979). These authors compared the effects of oral testosterone undecanoate (T.U.) administered at a dosage of 120 mg/day with matched placebo on the sexuality and endocrinology of twenty-nine impotent men. Thirteen men received T.U., sixteen received placebo. An improvement in sexual potency was reported by five of the patients who received T.U. compared with eight who were given placebo, therefore the authors concluded that testosterone administration had no effect on the sexuality of the impotent man. Interestingly, Benkert et al (1979) reported that the only signficant effect of T.U. treatment was to decrease the total plasma testosterone level (see Chapter 4).

An additional relevant, though uncontrolled study recently investigated the effects of administering mesterolone (a non-aromatisable synthetic androgen) at a dosage of 75 mg/day to 25 men presenting with "typical" secondary impotence (Cooper, 1980). Clinically the drug proved to be without significant benefits. (This is perhaps not a surprising finding, given that Luisi and Franchi (1980) reported mesterolone to be ineffective in improving the sexual

behaviour of a group of hypogonadal men). Again, as was the case in the Benkert et al. (1979) study, androgen administration did not act to increase plasma testosterone levels in Cooper's group of endocrinologically normal impotent men.

When one attempts to review the evidence for and against the efficacy of androgen administration in the treatment of erectile impotence one is faced with a dearth of adequately reported controlled studies. Remarkably, one is forced to conclude that, to date, not one study, using double blind assessment of behavioural response to androgen treatment compared with placebo, presenting evidence that the androgen administration resulted in a significant elevation in circulating androgen level has been published*. There is obviously a need for such studies to be carried out, (a) using men whose presenting complaint is erectile difficulty with no accompanying loss of sexual interest and (b) using men whose primary complaint is loss of, or reduced sexual interest.

*It is perhaps appropriate to state that Cooper et al. (1972) did successfully elevate circulating testosterone levels in five men complaining of erectile dysfunction using clomiphene, a non-steroid triethylene derivative, without any resultant beneficial effects on potency. However, clomiphene is an oestrogen antagonist, acting to inhibit the negative feedback to the hypothalamus by competing for and occupying hypothalamic oestrogen receptors. In the absence of appreciable levels of oestrogen (as is the case in the male) clomiphene can act as a weak oestrogenic agonist. Given that the inhibitory effects of oestrogens on male sexuality are well documented (e.g. Bancroft et al., 1974) any firm conclusions drawn from the results of the Cooper et al. (1972) study must be considered extremely suspect.

1.5 ANDROGENS AND NOCTURNAL ERECTIONS

The occurrence of periodic nocturnal erections in man was first described by Ohlmeyer et al (1944). These authors reported a recurrent eighty-five minute cycle of penile tumescence during sleep, each episode lasting for approximately twenty-five minutes. Eleven years later, Aserinsky and Kleitman(1955) noted that these episodes of nocturnal penile tumescence (NPT) tended to be coincidental with the rapid eye movement (REM) stage of sleep. Since then, a vast amount of research has been carried out investigating the NPT phenomenon, focusing particularly upon the possible use of NPT assessment as a diagnostic tool which could differentiate between organic and psychogenic forms of impotence (see Schiavi and Fisher, 1982 for review). However, the assumption that men whose erectile difficulties are due to psychological factors display "normal" NPTs and men whose impotence is due to organic factors display abnormal NPTSs has yet to be proven (Bancroft and Wu, 1980). Also, the psychogenic/organic distinction between different forms of impotence is not a clear cut one (Wasserman et al, 1980), and the equivalence of NPTs with erotically induced erections in the waking state has still to be established. (Bancroft, 1983 has suggested that the nocturnal erection may differ qualitatively from the conscious erotic erection is that the NPT episode may be brought about solely by activation of the venous shut-off mechanisms, i.e. no increase in arterial blood flow. This hypothesis would account for the slower rate of tumescence which is observed during the night. However, recent evidence has demonstrated that arterial blood flow in the penis is highly correlated with penile

circumference change during NPT episodes (Karacan et al. 1983). These authors conclude that the venous system, if it has a role in erectile function, must be supportive of the arterial system).

1.5.1 Androgen Levels during REM Sleep

Evans et al (1971) were the first investigators to report that testosterone levels reached a peak "in conjunction with or adjacent to" REM sleep phases. Miyatake et al (1980), however failed to find any mean difference in testosterone levels when they compared samples drawn from REM and non-REM sleep stages, using normal men as subjects. These negative findings were replicated by Roffwarg et al (1982), but using a more sophisticated form of analysis, these latter authors reported that the nocturnal peaks in testosterone concentration tended to be associated with the transition from non-REM to REM sleep. The authors suggest that abrupt elevations in testosterone levels may act to "prime" REM sleep processes. Conversely, it is possible that REM sleep in some way stimulates nocturnal testosterone production, as a recent study has shown that sleep deprivation acts to reduce circulating androgen levels in healthy young men (Cortes-Gallegos et al., 1983).

Given that there appears to be a relationship between testosterone and REM sleep, and that it has been estimated that 66-90% of all NPT episodes occur during REM sleep (Schiavi and Fisher, 1982), the possibility arises that a relationship may exist between testosterone and NPT episodes.

1.5.2 Androgen Levels during NPT Episodes

In 1977 Schiavi et al. reported the results of a study which looked at the relationships between NPT episodes, REM sleep and circulating testosterone levels in five normal men. The authors reported that abrupt elevations in circulating testosterone levels occurred during the night without a significant relationship to stage of sleep. However, mean testosterone levels during REM with tumescence were considerably raised compared with sleep periods free from REM and tumescence, suggesting a link between testosterone, REM and nocturnal erections. The authors then went on to look at the relationship between testosterone, NPTs and sleep patterns in normal men compared with men complaining of erectile impotence. Schiavi et al. (1982) reported that the two groups did not differ in terms of sleep parameters, mean tumescence time or frequency of NPT episodes. Again the authors found that the normal men had testosterone levels during REM with tumescence which were significantly elevated as compared with non-REM sleep stages without tumescence. The impotent men however had testosterone levels which did not differ when REM sleep with tumescence was compared with non-REM non-tumescence sleep. This result suggests that subtle differences may exist between impotent and normal men with respect to the interaction between androgens, sleep stage and nocturnal erections.

While reviewing the evidence for a relationship between androgens and nocturnal erections, it is fascinating to note that males during puberty demonstrate an abrupt elevation in total nocturnal tumescence time relative to REM (Schiavi and Fisher, 1982) which is coincidental

with the marked increase in circulating gonadotrophin and androgen levels which ocurs at this time (Rose, 1975).

1.5.3 Nocturnal Erections in States of Endocrine Dysfunction

Very little research has been carried out looking at the sleep patterns and NPTs of men with proven endocrine disorders. Wasserman et al. (1980) presented a case study of a patient who complained of progressive erectile impairment over a period of three years. This individual had his NPTs recorded in the laboratory for three successive nights and produced erections which fell within the normal limits with respect to penile circumference change from basal levels. However, rigidity judgements based on direct observation suggested that the erections produced were insufficient for vaginal entry. Subsequent clinical investigations revealed a massively elevated prolactin level which was treated with bromocriptine 10 mg/day. NPT assessment was repeated after five months of chemotherapy and the nocturnal erections were found to be improved and were judged as being sufficient for sexual intercourse. (Extrapolations from an uncontrolled single case study should, of course, be made with caution. In particular, in this case, the discovery of a likely physical basis for his sexual problem, followed by chemotherapy would probably have a profound psychological effect on the individual's sexual functioning and upon his subjective rating of his erection).

In a large scale screening study Cunningham et al. (1982) measured testosterone and prolactin levels in one hundred and seventy two men complaining of erectile impotence who underwent NPT assessment. Six men were subsequently found to be hypogonadal and six

hyperprolactinaemic. All of the hypogonadal men and five of the six hyperprolactinaemic patients were judged as displaying abnormal NPTs (in this particular study changes in penile circumference were not reported, abnormality was defined according to penile rigidity - if penile buckling occurred at less than 450g pressure the erection was considered incapable of vaginal entry and was classified abnormal). This study reporting that hypogonadal men have a marked impairment of NPTs has recently been replicated by Kwan et al. (1983). This is an important discovery, particularly in light of Bancroft and Wu's (1983) report that conscious erections in response to erotic films are relatively unaffected by androgen status in the hypogonadal man.

Cunningham et al, (1982) also made the intriguing observation that of twelve men complaining of erectile difficulties who were found to have testosterone levels which exceeded the upper limits of the normal range, eight displayed abnormal NPTs, (i.e. penile buckling occurred at less than 450g pressure). This finding suggests that both too low and too high a testosterone level may have inhibitory effects on nocturnal erections.

1.5.4 Administration of Androgens - Effects on Nocturnal Erections

1.5.4.1 The Hypogonadal Man

Kwan et al. (1983) recently presented the results of a small study where NPTs were recorded in six hypogonadal men "on" and "off" androgen replacement therapy. The authors reported that nocturnal erections were reduced in the untreated hypogonadal men, and were significantly increased following treatment with testosterone injections. This study is open to criticism on the grounds that portable home monitors were

used to measure the nocturnal erections and no objective data on sleep quality was collected. This study is in urgent need of replication.

1.5.4.2 The Eugonadal Man

The only published study in this area is that of Jovanovic and Tan-eli (1969) who compared the NPTs of impotent men before and after treatment with a methyltestosterone preparation. These authors reported that men complaining of erectile impotence had less frequent and less marked NPTs when compared with age matched controls, and that administration of the androgen preparation acted to normalise the NPTs.

Given the recent literature suggesting that most men presenting with erectile difficulties exhibit relatively normal nocturnal erections, coupled with the evidence against the efficacy of androgen treatment of erectile impotence (see section 1.4.2), this uncontrolled and inadequately reported study by Jovanovic and Tan-eli (1969) also needs to be replicated.

The outstanding questions in relation to androgens and NPTs to be tackled in this thesis are:-

(a) Do hypogonadal men display a reduced frequency, duration or amplitude of nocturnal erections, and are these NPTs improved following androgen replacement therapy?

(b) Are the NPTs of eugonadal men with erectile disorders (which are not obviously secondary to physical illness, e.g. diabetes) affected by high dosage testosterone administration?

1.6 Androgens and Cognitive Functioning

The study of cognitive sex differences has become one of the most controversial areas in the history of psychology. In the most authorative reivew of the literature to date, Maccoby and Jacklin (1974) came to the conclusion that there are only four valid and replicable sex differences in human behaviour; visuo-spatial, verbal, mathematical and aggression. The suggestion that human males and females may differ with respect to cognitive functioning has evoked fierce opposition, however Fairweather (1976) in his scathing review of sex difference studies is forced to concede "There is finally good evidence of a clear adult male superiortiy for a small nucleus of definitive spatial skills".

Spatial ability has been defined as the ability to visually manipulate images without the aid of verbal mediation (Petersen, 1975). Attempts have been made to explain why males demonstrate this slight but consistent spatial superiority, mostly arguing from an evolutionary perspective, e.g. reasoning that primitive man required superior visuo-spatial ability for hunting, etc. (Hamburg, 1974). Such propositions have been criticised (Nicholson, 1979) and as yet we have no satisfactory explanation for the almost universal demonstration of male superiority with respect to performance on spatial tasks.

The sex difference in spatial ability is one of particular interest to psychoneuroendocrinologists as it is a measure which shows clear differences which are generally reported as appearing at puberty (see below), which is coincidental with the pubertal increase in sex hormone level (Rose, 1975). Focusing on the male, spatial ability and

androgen status appear to parallel each other throughout adulthood, both increasing at puberty, then reaching a plateau, and there is evidence that there is a slight decline in spatial performance in later life (Likert and Quasha, 1970), and a similar decline in androgen level, particularly the "free" bio-active hormone fraction (Davidson et al, 1980; Vermeulen et al, 1972).

The observation that androgen level and spatial ability display this parallel pattern throughout the male life-span makes androgen status a possible physiological contributer to the observed variance in visuo-spatial skill.

It has also been proposed that tests of spatial ability merely tap general intelligence. While the solution of spatial tasks undoubtedly involves higher cognitive functioning, these tests cannot be simply measuring "g" as there are no reported differences between the sexes on tests of general intelligence (although females do demonstrate a slight but consistent verbal superiority over males, Maccoby and Jacklin, 1974) and correlations as low as 0.07 have been reported between performance on spatial and general intelligence tests (Paterson et al, 1930). (Recently however, Cooperman (1980) presented data suggesting that subjects who scored highly on spatial tests also performed better on tests of rote learning and verbal reasoning than poor spatial test scorers).

1.6.1 Biological and Environmental Determinants of Spatial Ability

Although the sex difference in spatial ability has been generally accepted, the causal factors which generate this disparity between the sexes have yet to be established.

Environmentalists propose that humans are reinforced differentially from birth, dependent on their sex, e.g. boys are given building blocks and construction kits as gifts while girls are given dolls and prams (Singleton, 1976). Therefore the environmentalist argument states that the spatial superiority demonstrated by the male is a result of developmental learning and experience. The major criticism that has been raised against this hypothesis is the well documented finding that the sex difference in spatial ability begins to appear at puberty (Broverman et al., 1968; Buffrey and Gray, 1972; Bock and Kalakowski, 1973; Harris, 1978; Maccoby and Jacklin, 1974; Rogers, 1976; Petersen, 1976; Waber, 1976; 1977(a); 1977(b); McGee, 1979). (Although recently it has been claimed that pre-pubertal sex differences may exist in spatial performance, Salkind (1976); Orsini et al., (1982)). The environmentalist hypothesis has also been criticised for lack of hard supportive evidence, e.g. "Evidence for differential socialisation in the development of visuo-spatial skills, too, is scanty and inferential at best.....While there is a clear difference in toy preference between the sexes, there is no evidence for any relationship between these preferences or modes of play and development of visuo-spatial skills in adulthood" (Burstein et al., 1980).

The ability to perform well at spatial tasks has been claimed to be a heritable trait (Vandenberg, 1968), but simple genetic explanations for the sex difference, such as sex-linkage on the X chromosome have generally been discredited (a) by the lack of consistent supportive evidence from parent-child correlations

(Boles, 1980) and (b) by the very poor spatial performance of sufferers of Turners (XO) syndrome (Money and Alexander, 1966).

One of the most intriguing hypotheses regarding the development of cognitive sex differences is that of Waber (1976; 1977a; 1977b) who proposes that the cognitive sex differences are due solely to the difference in the rate of physical maturation that exists between males and females (Tanner, 1978). Waber argues that in general males are superior on visuo-spatial tasks because they pass through puberty later than females, "Sex differences in mental abilities, it is argued reflect differences in the organisation of cortical functioning that are related to differential rates of physical maturation" (Waber, 1976). Evidence in support of the hypothesis is supplied by the author herself (Waber, 1976) and by Ray et al (1981). Fairweather (1976) however is critical of the hypothesis and suggests that substantial replication is necessary before it can be accepted, and Gordon and Galatzer (1980) point out that sufferers of Turners (XO) syndrome have prolongation of prepubertal maturation, yet demonstrate severe spatial deficits when compared with controls.

1.6.2 Androgens and Spatial Ability

One of the first reports which suggested an endocrine factor contributing to cognitive deficiency was that of Dawson (1967) who studied males feminised by a kwashiorkor-induced endocrine dysfunction. (Kwashiorkor is a desease of the liver resulting from protein deficiency in infancy, which prevents the inactivation of the normal amount of oestrogen present in the male). Dawson discovered that kwashiorkor affected males as adults demonstrated impaired spatial

ability and were more field dependent than normal control males. However, one must always remember the strong environmental contributions in such cases, e.g. Masica et al. (1969) demonstrated that males with the testicular feminising syndrome of androgen insensitivity scored in the feminine or masculine direction on psychological tests depending on the sex they were brought up as.

Preliminary research has been carried out using endocrinologically normal populations in an effort to investigate the role androgens play (if any) in the regulation of cognitive functioning (Broverman et al., 1968; Klaiber et al., 1967; Petersen, 1976). These investigators, using a correlational approach, came to the conclusion that in males, low androgenisation is correlated with good spatial performance and vice versa. This is an interesting, if slightly puzzling finding. It is possible that an optimal level of circulating androgen is necessary for optimal spatial performance, but androgen levels above this threshold level may have an inhibitory effect (recently just such a hypothesis has been proposed, focusing instead on the optimal oestrogen level, Nyborg 1983). However, as McGee (1979) points out the measures of androgenicity that were used in the Broverman et al. (1968) and Petersen (1976) studies were far from satisfactory. Ratings were made from photographs, pubic hair and muscular development were scored, and these scores represented the subjects androgenicity index which was then correlated with performance on visuo-spatial tasks. To quote McGee (1979) "Until more direct methods of hormonal assay are employed on larger samples, the precise nature of the relationship between spatial ability and hormonal balance will remain an open question".

The findings of Broverman et al. (1968) and Petersen (1976) are made to appear even more suspect in light of the data supplied by Krause and Hintze (1980) who correlated fifty-two typical signs of masculine differentiation with circulating androgen levels in one hundred and twenty-nine healthy young men. Krause and Hintze (1980) came to the following conclusion, "Stages of body hair are obviously independent from actual androgen plasma levels. Also body proportions and size of the genital organs are not correlated to hormone levels". In accommodating this data, Broverman et al. (1980) recently stated, "Blood levels of the gonadal hormones are poor indicators of degree of hormonal stimulation, metabolic clearance and production rates of the gonadal hormones seem to be more closely related to anthropometric indices of gonadal hormone stimulation and to cognitive and affective functioning". In investigating gonadal hormone clearance rates, Klaiber et al. (1967) measured 17-ketosteroid excretion in adult males and reported a significant correlation between this measure and spatial test scores. However, Farr (1978) in a recent replication failed to find any significant relationship between 17-ketosteroid production, selected anthropometric measures and cognitive functioning.

Perhaps the most exciting study to have been published to date concerning the relationship between hormones and cognitive functioning is that of Hier and Crowley (1982) who investigated the spatial ability of hypogonadal men. These authors compared the spatial performance of men who had idiopathic hypogonadotrophic hypogonadism (I.H.H.) with

controls and with men who had acquired hypergonadotrophic hypogonadism (A.H.H.) after puberty. The patients with I.H.H. displayed markedly impaired spatial ability when compared with the A.H.H. and control groups, and spatial performance was positively correlated with testicular volume in the I.H.H. group. This evidence supplied by Hier and Crowley appears to be in opposition to the Waber hypothesis(see section 1.6.1) concerning the generation of the sex difference in spatial ability as the I.H.H. men, is common with sufferers of Turners (XO) syndrome have prolongation of pre-pubertal maturation, yet have markedly impaired spatial ability.

Bancroft and Wu (1983) investigated the effects of androgen replacement and withdrawal on erectile response to erotic fantasy and to erotic film in hypogonadal men, and found that only the ability to produce erections in response to erotic fantasy appeared to be dependent on androgen status. As Bancroft (1980) states, "Mental imagery is an active visuo-spatial process, it is possible that androgens may facilitate this process and hence facilitate erotic imagery in a relatively non-specific way". However, Rubin et al. (1979) and Lange et al. (1980) found that testosterone levels were highly correlated with penile diameter changes in response to erotic film using eugonadal subjects, and Hier and Crowley (1982) reported that three months of androgen replacement therapy did not result in

improved spatial performance in six hypogonadal men. (Hier and Crowley (1982) did point out that because of the small sample size, a slight but significant improvement in test scores with androgen treatment cannot be ruled out, leaving the effects of androgen administration on cognitive performance in men an area requiring further study).

In this thesis the following questions are addressed in an effort to further investigate the relationship between androgens and cognitive functioning in men:-

(a) Does the spatial performance of the hypogonadal men improve following longterm androgen replacement therapy?

(b) Does raising the circulating level of androgens above the normal range have an effect on the spatial performance of the eugonadal man?

1.7 ANDROGENS AND PERSONALITY

Apart from the interest shown in the possible relationship between androgens and cognitive functioning, very little research has been carried out looking at whether androgens are related to various other aspects of personality in man.

Those personality measures which have received most attention are the personality dimensions of Hans Eysenck and the Sensation Seeking Scale of Marvin Zuckerman. In this section the research carried out to date equating these behavioural measures with androgen levels will be briefly reviewed.

1.7.1 The Eysenck Personality Dimensions

Over the last thirty years H.J. Eysenck has developed and refined a series of self-report inventories which he claims classify individuals in terms of three dimensions of personality, namely

extraversion (E), neuroticism (N) and psychoticism (P). Of these three dimensions, the newest, and for our purposes the most interesting, is the psychoticism or P scale. (It is perhaps appropriate to point out that Eysenck's definition of psychotism differs somewhat from the standard psychiatric definition of the term. A high P scorer is not described as being insane, but rather as being solitary, insensitive, hostile and lacking in feeling and empathy, Eysenck (1978)).

Eysenck has repeatedly proposed that this dimension is in some way related to androgen levels in man, e.g. "It seems likely that the biological basis of P will be found to be closely related to male sex hormones" (Eysenck and Eysenck, 1975). "The fact that males have much higher P scores than females suggests that the androgen/oestrogen balance will be involved" (Eysenck and Eysenck, 1976). "High P scorers are also very strongly determined in their behaviour by genetic factors, and this is probably mediated by male hormones" (Eysenck and Wilson, 1979). In his book "Sex and Personality" (Eysenck, 1978) the author cites the work of Daitzman (1976) who attempted to correlate endogenous steroid hormone levels with various psychometric test measures. With regard to psychoticism, Daitzman reported positive but insignificant correlations with androgen level. Eysenck appeared to be undaunted by this lack of significant association between psychoticism and androgens stating "These results, given the small numbers involved and the pioneering nature of the experiment, tend to fit in quite well with our conceptualisation" (Eysenck, 1978). In a more recent study, Daitzman and Zuckerman (1980) again failed to find any relationship between circulating testosterone levels and psychoticism in young men.

In fairness to Eysenck, in neither of these studies (Daitzman, 1976; Daitzman and Zuckerman, 1980) was the Eysenckian measure of psychoticism, namely the P scale used.

Only one study known to the present author has looked at the effect of exogenous androgen administration on measures of personality in man. This was a study by Kaiser et al. (1978) who carried out a controlled double blind behavioural comparison of androgen versus placebo in ageing males. Half of the sixty-six subjects received mesterolone 75 mg/day for five weeks, half received matched placebo. The authors claimed that the active medication acted to reduce "psychovegatative symptomatology" and resulted in a decrease in neuroticism and an increase in extraversion scores. (P scores were not evaluated, as the authors used an earlier version of Eysenck's personality test, the EPI as opposed to the more recent EPQ, (Eysenck and Eysenck, 1975)). These beneficial effects of mesterolone are surprising, given that at double the dosage used in the Kaiser et al. (1978) study, Luisi and Franchi (1980) found mesterolone ineffective in the treatment of hypogonadism, whereas another androgen preparation (testosterone undecanoate) was shown to be highly efficacious in a group of patients where androgen-behaviour relationships are usually demonstrated most clearly (see section 1.3).

1.7.2 The Sensation Seeking Scale

In 1964 Zuckerman et al. developed a self-report inventory which they claimed measures a set of behaviours described as "sensation seeking" (a sensation seeker is described as someone who actively seeks stimulation and excitement, roughly equivalent to an Eysenckian

impulsive extravert). A series of studies have been published which indicate that the Sensation Seeking Scale (SSS) is a reliable, valid and useful measure (see review by Zuckerman, 1979). The SSS is of particular interest in light of recent evidence which suggests that a positive correlation exists in the eugonadal man between SSS scores and gonadal hormone level (Daitzman et al., 1978 Daitzman and Zuckerman, 1980). In an attempt to explain this finding Zuckerman has formulated a hypothesis which proposes that elevated gonadal steroid levels may act to reduce mono-amine oxidase activity which leads to an increase in central nervous system mono-amine levels which would in turn facilitate neural transmissions and perhaps stimulate sensation seeking behaviour (Zuckerman, 1979; 1983; Zuckerman et al., 1980). This is an interesting, if slightly speculative hypothesis. To date all the evidence in favour of this hypothesis has been derived from correlational studies, equating endogenous steroid levels with behaviour in the eugonadal man. A better method of testing the hypothesis that gonadal hormone levels are causally related to sensation seeking behaviour would (in the opinion of the present author) be to look for behavioural changes brought about as a result of exogenous androgen administration. If the Zuckerman hypothesis is valid, this endocrine manipulation should lead to an increase in sensation seeking behaviour, which in turn should be reflected in SSS scores. Similarly the hypothesis should predict that hypogonadal men, on account of their markedly reduced circulating gonadal steroid levels, should produce reduced SSS scores which increase following androgen replacement therapy.

1.8 ANDROGENS AND AGGRESSION

1.8.1 Androgens and Aggression in Animals

Evidence derived from research carried out in animals in general suggests that a relationship exists between androgens and aggression in the male, e.g. in the adult male mouse castration decreases and testosterone replacement increases the frequency of bouts of inter-male aggression. Also fighting among intact males usually begins to appear about the time of puberty, as androgen levels in the blood are rising, however pre-pubertal inter-male fighting can be induced by injections of testosterone (Bronson and Desjardins, 1971). It is important to stress, however, that species differences exist in hormone mediated effects on aggressive behaviours. As we ascend the phylogenetic scale, social experience appears to play a major role in determining aggressive responses to castration and androgen replacement. Dixon and Herbert (1977) observed a group of Talopoin monkeys and reported that castrate males were sometimes more highly ranked than intact males and that testosteorne administration acted to increase the aggressive behaviour of these castrates, but only directed against more subordinate males. The authors conclude that previous social experience influences androgen induced aggressiveness. Certainly, the strong direct relationship between androgens and aggression observed in rodents does not appear in the study of non-human primates (Benton, 1981).

It is also important to emphasise that "aggression" is a broad descriptive term encompassing various types of specific behavioural response which can be classified as aggressive, e.g. predatory,

inter-male, fear induced, irritable, maternal, sex related and instrumental (Moyer, 1976). It is also probable that different gonadal hormones have differing effects on these sub-factors of aggressive behaviour, e.g. androgens and oestrogens have markedly similar effect on reintroducing displays of sex related aggression in castrate red deer stags, but only androgens act to stimulate bouts of inter-male social aggression which determine dominance hierarchies (Fletcher and Short, 1974; Fletcher, 1978).

1.8.2 Androgens and Aggression in Man

Detailed evidence regarding the behavioural consequences of castration in the adult human male is lacking, but it is generally thought that the major effect of the operation is to reduce the level of libido of the castrate man, with no appreciable effect on non-sexual aggressive behaviours (Rose, 1978). The evidence that in the human male castration always leads to a decrease in sexual drive has not, however, been completely demonstrated (Heim and Hursch, 1979). Relatively little attention has been given to the influence of castration on human aggression of a non-sexual nature, although in a study of the behavioural effects of castration in two hundred and forty-four men, Bremer (1959) concluded that castration is an inappropriate treatment for human aggressive behaviour.

In the human it is of interest to note that most acts of violent aggression are committed by young men, and that such actions become progressively rarer with advancing age (Eysenck and Eysenck, 1976) and that androgen levels are highest in young men and decline with age (Davidson et al., 1980; Pirke et al, 1981; Vermeulen et al., 1972),

but as with sexual behaviour there is no evidence of a causal relationship between the two variables.

Uncontrolled clinical reports have suggested that withdrawn psychiatric patients could be made more outgoing, and aggressive patients made even more violent by androgen treatment (Strauss et al., 1952; Sands and Chamberlain, 1952). However, serious attempts at investigating possible androgen/aggression relationships only began approximately twelve years ago. In one of the first of these studies, Persky et al., (1971) reported a significant correlation between aggression (as measured using the Buss-Durkee Hostility Inventory, Buss and Durkee, 1957) and testosterone production rate in young men. Meyer-Bahlburg et al. (1974) attempted to replicate this study using a very similar experiment design but failed to find the association claimed by Persky et al (1971). Both these studies can be criticised because of the experimental procedure employed. In an effort to determine testosterone production rate, radioactive testosterone was infused into the systemic circulation of each man as they completed behavioural questionnaires and had serial blood samples taken. In effect, measures of behaviour were being made in an attempt to relate them to endogenous testosterone levels, while exogenous testosterone was being infused.

Doering et al., (1974) and Monti et al., (1977) also failed to find any relationship between Buss-Durkee rated aggressive behaviour and mean testosterone level in normal young men. In light of this evidence suggesting a lack of association between testosterone and aggression in normal men, investigators began to look for possible

relationships in behaviourally extreme populations.

Using male prisoners as subjects, Kreuz and Rose (1972) reported that mean testosterone levels correlated neither with the incidence of observed fighting behaviour, nor with various questionnaire measures of aggression. However, the authors did make the fascinating observation that the earlier the age of first conviction for violent crime, the higher the mean plasma testosterone level at this later age. In a similar study using a prison population, Ehrenkranz et al., (1974) (who had several years personal knowledge of the prison population and were thus able to divide the prisoners into specific behavioural categories) reported that a group of very aggressive prisoners had mean testosterone levels which were significantly elevated in comparison with a group of "typical" prisoners. Interestingly a group of socially dominant though non-aggressive prisoners also had higher testosterone levels than control prisoners. It is important to note that the Buss-Durkee Inventory and other psychological tests did not discriminate between these three categories of prisoners. In contrast, Matthews (1979) found no difference in mean testosterone levels when he compared violent prisoners with non-violent prisoners, matched for age, height, weight and length of time spent in prison. In a study of men who were aggressive specifically in a sexual situation, Rada et al (1976) reported that violent rapists had higher testosterone levels than non-violent rapists or normal controls. This result fits in well with the theorising of Brain (1981) who suggests that androgens may be related specifically to sexual aggression, and he cites the work of Hawke (1950) who proposed that castration may be an effective means of

curbing violence in sex offenders. Reports have also been made claiming that pharmacological antiandrogens are effective in reducing aggression in sex offenders (Laschet, 1973; Laschet and Laschet, 1975).

More recent studies have provided additional evidence suggesting a possible relationship between testosterone and aggression in man. Using sport as a situation where societal constraints on aggressive behaviour are temporarily lifted, Scaramella and Brown (1978) reported that male hockey players whom the team coach rated as being the most aggressive when provoked had the highest testosterone levels. This was an interesting finding, but as only one blood sample was taken per subject, and only fourteen subjects were studied, the results must be interpreted with caution. However, they have been to a certain extent substantiated by Olweus et al. (1980) who carried out a study of adolescent Norwegian males. The authors correlated mean plasma testosterone with various behaviours which were assessed mainly by inventories. They found a significant correlation between testosterone and self-reported physical and verbal aggression, "mainly reflecting responsiveness to provocation and threat" (Olweus et al., 1980). These findings were replicated by Mattson et al. (1980) in a population of institutionalised male deliquents.

1.8.3 Methodological Problems in Androgen-Aggression Research

When reviewing the studies to date in this area, three major methodological problems involved in this type of research become apparent:-

1.8.3.1 Measurement of Human Aggression

Most of the studies cited above have relied on the Buss-Durkee Hostility Inventory to assess aggressive behaviour. As Rose (1975) points out, scores on this self-report questionnaire do not appear to relate to observed aggressive behaviour, "If there are significant correlations between aggression and testosterone in humans, we need much better methods of assessing various aspects of behaviour than are currently available" (Rose, 1975).

1.8.3.2 Blood Sampling Methodology

As outlined in section 1.4.1 it is essential that several blood samples be taken from each subject because of the high degree of intra-individual variation in circulating testosterone levels that exists in the adult human male. This allows the investigator to arrive at a representative mean hormonal value for each individual to correlate behavioural measures against. Unfortunately, single blood samples have been used to determine androgen status in most of the studies carried out to date.

1.8.3.3 Cause-Effect Relationships in Androgen-Aggression Research

Many investigators in this field of research have carried out correlational studies, assuming that if a relationship between testosterone and aggression does exist, then it is the hormone which in some way "causes" the aggressive behaviour. It is vitally important to bear in mind that the expression of aggressive behaviour may have a marked effect on the endocrinology of the human male, e.g. Elias (1981) has demonstrated that male wrestlers exhibit significant elevations in circulating testosterone levels during wrestling bouts (interestingly

winners displayed greater testosterone increases from basal levels than losers) and Mendelson et al. (1982) have recently shown that LH (i.e. the major stimulant for testosterone production) levels were found to be elevated in postmortem blood samples obtained from men who sustained sudden and violent deaths. Thus (to take a hypothetical example), if a sub-group of highly aggressive prisoners were shown to have very high circulating testosterone levels, it is possible that the elevated androgen is a result of the aggressive behaviour rather than the cause (Archer & Lloyd, 1982).

In summarising the evidence for and against androgens playing a role in the expression of aggressive behaviour in the adult human male, the present author would tend to agree with Rose (1978) who states "It is obvious that the question remains unanswered but some suggestion of a relationship appears consistent with the results obtained to date". It is surprising that virtually all the investigators in this area have relied on the correlational approach for data collection. Experimental manipulation of androgen levels using behaviour as the dependent variable would appear to be the best method of gaining evidence to test the hypothesis that a relationship exists between androgens and aggressive behaviour in man.

CHAPTER 2

GENERAL MATERIALS AND METHODS

2.1 BEHAVIOURAL ASSESSMENT

In order to arrive at a detailed and accurate assessment of any changes in behaviour which are brought about as a result of androgen administration, three methods of behavioural measurement have been employed in the studies described in this thesis:-

(a) self report diary data

(b) interview ratings

(c) psychophysiological measurement

2.1.1 Daily Diary Ratings

Sexual Behaviour

Self report data is often criticised as being "unscientific" and not amenable to objective verification (Allen and Potkay, 1973). However, as Barlow (1977) points out, self report of sexual function and dysfunction may be more important than behavioural and physiological measures, because in adult patients self report of the dysfunction is often the only necessary criterion for entry into treatment. Similarly self-assessment of progress is often the major criterion for terminating the intervention.

Each of the subjects who were studied were asked to complete a daily diary form (see Appendix IV) assessing their sexual behaviour. This diary was based on that used by Skakkebaek *et al.* (1981) in their study of the effects of androgen replacement on the sexuality of the hypogonadal man. The diary was modified in that subjects were asked to record whether sexual activity was self, partner or jointly initiated. Subjects were also asked to provide daily (as opposed to weekly) ratings of frequency of sexual thoughts and sexual arousal associated with these thoughts, on two separate visual analogue scales (see below). It was important to collect sexual behaviour data on a daily

basis, as it has recently been demonstrated that retrospective (monthly) estimates of behaviour, e.g. frequency of awakening with an erection, correlate poorly with daily records (Reading et al., 1982; Reading, 1983).

Mood State

As a great deal of research has (and is) been carried out testing the general hypothesis that endocrine changes influence mood state in women (e.g. Sanders et al. 1983), it was considered appropriate to also investigate the effects of androgen administration on mood state in the man.

In order to quantify mood change, a series of ten visual analogue mood scales were incorporated into the daily diary assessment form. These were based upon the mood scales devised by Sanders (1980) and have been cross-validated with Lorr-McNair MACL scores (McNair and Lorr, 1964) by Sanders (1980). Visual analogue scales have the advantage of being simple, concise, quick to complete and are not influenced by response sets (Bond and Lader, 1974). The analogue nature of the scale avoids imposing artificial digital categorisation of moods and feelings (Mackay, 1980). Data from visual analogue scales are suitable for both parametric and non-parametric techniques of statistical analysis (Maxwell, 1978). Data from analogue scales cannot be compared inter-individually (Pirke and Kockott, 1982); however, they do appear to be suitable for quantifying intra-individual changes (Aitken, 1969; Zealley and Aitken, 1969; Folstein and Luria, 1973; Bond and Lader, 1974; Maxwell, 1978; Peck and Dean, 1983).

Standardisation of Visual Analogue Scores

In order to combine data from groups of subjects to graphically portray and compare results, a method of standardising the visual

analogue scores was developed. As individuals vary as to where they centre themselves on the 100 mm scale, and also vary as to the range of the scale they use to represent swings of mood, raw means and standard deviations are inappropriate. To control for this between subject variation, scores were standardised by expressing the difference between each subject's treatment phase score and his overall entire study phase mean score as a percentage of the range of the scale used by that individual. This method of standardisation of visual analogue data was suggested by Maxwell (1978). To illustrate this method of standardisation, a simple hypothetical example is outlined below.

Two subjects are treated with Drug A for three days and placebo for three days. Subjects rate themselves on a daily visual analogue scale labelled "Energetic". The raw scores are given below.

	Daily Visual Analogue Ratings					
	Placebo			Drug A		
Subject No.1	30	40	50	60	70	80
Subject No.2	13	15	18	22	25	26

As can be seen, both subjects appeared to rate their energy level as higher during active treatment. However, one cannot say that Subject No.1 reported a greater effect than Subject No.2 as he may have centred himself differently on the 100 mm scale and used a wider range of the scale to reflect changes in mood.

Using the standardisation method outlined above, one calculates the overall mean score for each individual over the six day study period, and the range of the scale used by that individual (maximum

minus minimum score). For Subject No.1, mean = 55, range = 50; for Subject No.2, mean = 19.8, range = 13. Standardised scores are obtained by calculating the difference between each subject's raw score and his overall mean score and expressing this difference as a proportion (percentage) of the range of the scale used by that individual. The standardised scores are given below.

	Daily Visual Analogue Ratings					
	Placebo			Drug A		
Subject No.1						
Raw Scores	30	40	50	60	70	80
Standardised Scores	-50	-30	-10	+10	+30	+50
Subject No.2						
Raw Scores	13	15	18	22	25	26
Standardised Scores	-52	-37	-14	+17	+40	+48
	Mean Standardised Score -32%			Mean Standardised Score +32%		

Therefore in our hypothetical example using the proportional method of standardisation of visual analogue scores we summarise the data from the two individuals by concluding that Drug A brought about a mean 32% increase in self-rated energy.

However, it is important to stress again that visual analogue data is not appropriate for between subject comparison. This standardisation procedure was devised so as to enable the author to combine data from individuals in order to graphically present results for groups of subjects.

2.1.2 Interview Assessment

A structured interview rating of sexual functioning (see Appendix V) was carried out by the author at the end of each of the androgen and placebo treatment periods in the studies on the eugonadal men complaining of reduced sex interest (Chapter 5) and erectile dysfunction (Chapter 6). This interview assessment was in addition to the daily diary self-ratings. The interview (see Appendix V) was based on that used by Bancroft et al. (1982). Blind ratings were made of sexual functioning during the preceding treatment period. Ratings were made of intercourse and masturbation frequency, level of sexual interest, positive and negative feelings during sexual contact, non-genital arousal during sexual contact, orgasm frequency, quality of erection, degree of ejaculatory control and receptivity (i.e. the subject's response to partner initiated sexual contact).

2.1.3 Psychophysiological Assessment

In addition to the self ratings and interview ratings of sexual behaviour, a laboratory method, directly measuring nocturnal erections, was included in the experimental design of the studies carried out on the hypogonadal man and the eugonadal man complaining of erectile dysfunction. In both studies, nocturnal erections were measured "on" and "off" androgen treatment. The details of the measurement of nocturnal erections are described in Chapter 7.

2.2 ENDOCRINOLOGICAL ASSESSMENT

In each of the studies described in this thesis, 10 ml blood samples were collected into lithium-heparin tubes. Plasma was separated by centrifugation at 700g for ten minutes at 4°C. Plasma was stored at -20°C prior to assay.

2.2.1 Testosterone

Testosterone was measured using the method of Corker and Davidson (1978). 50 ul aliquots of plasma and 50 ul of phosphate buffered saline (PBS) were extracted with 1 ml hexane-ether 4:1 (v/v). After freezing of the aqueous phase, the organic layer was tipped off into assay tubes. The organic layer was taken to dryness under nitrogen at 40°C and reconstituted in 100 ul PBS. The extraction procedure resulted in recovery of 85-92% (n=30) of 1,000 cpm of 1α,2α ^{3}H-testosterone (Amersham International). Therefore for all calculations an adjustment multiplication constant of 10/9 was introduced.

The extracted samples were then assayed in duplicate using an antiserum (E01, supplied by Dr. S. Tillson) which was raised in the goat against testosterone-3-carboxymethyloxime BSA. The antiserum showed significant cross-reaction only with 5α-dihydrotestosterone (23.9%) and was used at an initial dilution of 1:10,000. 1α,2α -^{3}-testosterone was used as a tracer. Standards of testosterone were obtained from Steroloids Inc. and assayed in a reference curve of 20-640 pg/ml. All ^{3}H assays were counted on a Packard Tri-cab liquid scintillation spectrometer. The inter and intra coefficients of variation for the testosterone assay were 9% and 6% respectively.

2.2.2 Dihydrotestosterone

5α Dihydrotestosterone (DHT) was measured using a modification of the method of Thorneycroft *et al*. (1973). After addition of 1,000 cpm ^{3}H-DHT (New England Nuclear) to act as a recovery check, 200 ul of plasma was extracted with 2 ml hexane-ether 4:1 (v/v). After freezing of the aqueous phase, the organic layer was taken to dryness under

nitrogen at 40°C in a fresh tube and 500 ml iso-octane added. Chromatographic separation of DHT from testosterone and other steroids was carried out on celite columns which were made up from 5 ml Kimble disposable pipettes (Owens, Illinois, U.S.A.). Column flow was restricted with a glass bead.The columns were filled with 5 cm of a well mixed quantity of 1 gm celite and 0.5 ml ethylene glycol. The column was washed with 10 mls iso-octane prior to use. Elution of DHT from the column was achieved using 3.5 ml 5% benzene/iso-octane. The resulting eluate was dried down under nitrogen at 40°C and reconstituted in 200 ul of PBS, 50 ul of which was used as a recovery check for each sample (mean value 69%) and 100 ul used for radioimmunoassay. Assay standards were obtained from Steroloids Inc. The DHT antiserum (171) was raised in the rabbit to 5 dihydrotestosterone-3 carboxymethyloxime-BSA by Mr. D.W. Davidson (MRC Reproductive Biology Unit, Edinburgh) and was used at a dilution of 1:6,000. The only significant cross-reaction was with testosterone (57%). The radioimmunoassay procedure was as described for testosterone by Corker and Davidson (1978) with a standard curve from 5-320 pg/ml. The inter and intra coefficients of variation for the DHT assay were 14% and 9% respectively.

2.2.3 Sex Hormone Binding Globulin

Sex Hormone Binding Globulin (SHBG) was measured using a modification of the method of Anderson et al. (1976). This assay utilises DHT as a high affinity ligand, and the competition between DHT and ^{3}H-DHT reflects the relative SHBG concentration of the plasma sample.

250 ul plasma samples were diluted 1:8 with 1.75 ml phosphate buffer. Standard solutions Y and Z were made up, Y containing 100 ul

2.5 ug/ml DHT and 100 ul 25 uCi/ml ^{3}H-DHT made up to 50 ml with phosphate buffer. Standard solution Z was made up as above, but with 50 ul 2.5 ug/ml DHT instead of 100 ul. Six tubes were set up for each plasma sample, two total counts (TC) tubes, two Y labelled tubes and two Z labelled tubes. To the TC tubes 40 ul of 2.5 ug/ml DHT solution was added and dried down under nitrogen at 40°C. The TC and Y labelled tubes then had 300 ul of solution Y added, and the Z labelled tubes had 300 ul of solution Z added. All six tubes then had 200 ul of the diluted plasma sample added. The contents were then briefly rotamixed and allowed to incubate at room temperature for 30 mins prior to overnight storage at 4°C. The following day, tubes were transferred from the fridge to an ice-water bath, and to one tube at a time, while rotamixing to avoid high local salt concentrations, 0.5 ml saturated ammonium sulphate was added to precipitate the protein. Tubes were then left in the ice-water bath for a further 30 mins and then centrifuged at 3,000g and 4°C to sediment the precipitate. The supernatant was then decanted into scintillation mini-vials (Sterilin Ltd.), 2 ml scintillation fluid added, vials were then stoppered and briefly rotamixed and placed inside glass scintillation vials and counted in the ^{3}H-scintillation spectrometer, after several hours equilibration.

SHBG concentrations were calculated by subtracting the mean Y value from the mean TC value, multiplying the difference by 100 and dividing the result by the mean TC value. This figure was then multiplied by the molar concentration constant which was 0.221 for the Y solution and 0.118 for the Z solution. The average of the final Y and Z values represented the SHBG binding site concentration of the plasma sample, X 10-8M. To convert this value to nmol/l the result

was multiplied by 10. The inter and intra coefficients of variation of the SHBG assay were 9% and 8% respectively.

2.2.4 Gonadotrophins

LH and FSH were measured in duplicate using the specific double antibody radioimmunoassay described by Hunter and Bennie (1979). Antisera to human LH and FSH were raised in the rabbit and kindly supplied by Professor W.R. Butt, Birmingham. ^{125}I-labelled LH was prepared from h-LH IRC-2 (Dr. A. Stockell, Hartree, Cambridge) and ^{125}I-labelled FSH from highly purified h-FSH (Professor Butt) according to the method of Hunter and Bennie (1975). Cross-reactivity with other hormones is described by McNeilly and Hagen (1974). After incubation, tubes were centrifuged for 30 mins at 4°C and 1,500g, the supernatant poured off and the precipitate containing antibody-bound hormone counted in an LKB-Wallac gamma counter.

The inter and intra coefficients of variation for the LH assay were 13% and 9% and for the FSH assay 11% and 8% respectively.

2.2.5 Prolactin

Plasma prolactin was measured by a double antibody radioimmunoassay described by McNeilly and Hagen (1974). Highly purified human prolactin was kindly supplied by Dr. H. Friesen (Manitoba). Prolactin was iodinated to a specific activity of 40-80 uCi/ug by a modification of the chloramine-T method and purified by column chromatography on Sephadex G-100 (40 x 2.2 cm). The antibody to prolactin was raised in the rabbit by Dr. A.S. McNeilly (Edinburgh). 50 ul samples were diluted with 450 ul 0.05 M barbitone, pH 8.6 containing 2.5% BSA (BDH) and 50 ul antiserum (1:12,000 dilution). Tubes were then incubated for 24 hrs at 4°C. After addition of ^{125}I-prolactin (50 ul; 200-500 pg) incubation was continued for

24-48 hrs at 4°C, when antibody-bound and free hormone were separated by the second antibody (as described in detail by McNeilly and Hagen, 1974) with a further incubation for 16-24 hrs at 4°C. Tubes were then centrifuged at 1,500g for 30 mins, supernatant tipped off and the precipitate containing bound hormone counted in an LKB-Wallac gamma counter.

The inter and intra coefficients of variation for the prolactin assay were 12% and 9% respectively.

2.3 INTERDEPENDENCE OF HORMONE-BEHAVIOUR VARIABLES

In the studies reported in this thesis we are manipulating the endocrine status of men and monitoring any resultant behavioural changes, i.e. behaviour is being used as the dependent variable. Using properly controlled experimental methodology, this would appear to be a valid and appropriate method of tackling many of the unresolved problems in this area. However, it is important to note that several researchers have reported that the expression of sexual behaviour may affect the neuro-endocrine system in man, e.g. an anonymous investigator claimed that his beard growth (a proposed bio-assay of testosterone production) increased during periods when he was anticipating returning to his sexual partner after prolonged separation (Anon., 1970). However, Hunter et al. (1983) have recently reported a lack of association between beard growth and serum testosterone levels. Turning to the effects of sexual arousal on the androgen status of the human male, Lincoln (1974) measured plasma testosterone and LH levels in men during and after exposure to erotic films, and he reported no effect. Pirke et al (1974) in a very similar study demonstrated a delayed effect; several hours after watching the erotic films the subjects displayed a slight elevation in circulating testosterone

levels.

Focusing on the effect of sexual activity on endocrine measures in the human male, Fox et al. (1972) reported that plasma testosterone levels were elevated in one man prior to, and following coital orgasm. The same authors also reported that masturbation had no significant effect on plasma testosterone levels. However, Purvis et al. (1976) claimed that masturbation led to an increase in testosterone levels whereas Stearns et al. (1973) found no hormonal changes following orgasm during coitus or masturbation.

Given these opposing findings, no conclusions can be made as yet regarding the effect of sexual arousal and activity on hormonal measures in men, but as Hatch (1981) states, a complex bidirectional relationship may exist between gonadal hormones and sexual behaviour in man, sexual behaviour being partly determined by hormone levels and certain sexual behaviours possibly playing a role in determining plasma concentrations of some gonadal hormones.

CHAPTER 3

THE BEHAVIOURAL EFFECTS OF VARYING THE REPLACEMENT DOSE OF TESTOSTERONE IN THE HYPOGONADAL MAN - A CONTROLLED EXPERIMENT

3.1 INTRODUCTION

Preliminary evidence has been presented which suggests that a dose-response relationship exists between androgen replacement and sexual behaviour in the hypogonadal man (Davidson *et al.* 1979; Salmimies *et al.* 1982). However, these studies are open to criticism (see Section 1.3.2). Double-blind experiments using adequate control over androgen replacement leading to physiological levels of circulating testosterone have yet to be carried out, e.g. Davidson *et al.* (1979) point out that the intra-muscular depot injections that have been used in the studies to date lead to supra-physiological testosterone levels in the few days following administration. It could be argued that any resultant behavioural changes are thus due to a pharmacological rather than a true physiological effect.

The study reported in this chapter was designed in an attempt to investigate further the relationship between androgen replacement and effects on specified aspects of sexual functioning and mood in the hypogonadal man, and is in effect a direct extension of the work carried out by Salmimies *et al.* (1982).

3.2 Materials and Methods

3.2.1 Subjects

Male hypogonadal subjects were recruited from the endocrine clinic at the Western General Hospital in Edinburgh. Between October 1981 and December 1982 the author searched the endocrine out-patient clinic files on a weekly basis, and all hypogonadal clinic attenders were

offered a place in the study. Prospective subjects were informed by the clinician that we were carrying out research on a new oral form of testosterone replacement therapy, and that we were keen to monitor the behavioural effects of varying the dose. Patients who were interested were referred to the author who explained the study in detail. Subjects were informed that they would be investigated thoroughly and that this would involve fortnightly blood sampling and the completion of daily diary forms assessing sexual functioning and mood state throughout the five month study period. The subjects were assured of confidentiality and that the results would be extremely valuable from a research point of view, and would also enable us to make firm recommendations regarding the most suitable long-term replacement dose of testosterone for them as individuals.

Ten hypogonadal men agreed to participate in the trial and were recruited. Unfortunabely, two subjects dropped out at an early stage, one because he experienced difficulty swallowing the capsules and the other because he refused to continue completing the diary assessment forms. Complete behavioural data was therefore collected for eight hypogonadal men. Patient characteristics are shown in Table 3.1.

3.2.2 Androgen Preparation

The natural form of the major testicular androgen, testosterone, cannot be administered orally as it is rapidly metabolised by the liver (Kloer et al. 1980; Nieschlag and Frieschem, 1982). As a result, in general clinical practice, testosterone must either be injected intramuscularly or implanted sub-cutaneously (or less frequently,

TABLE 3.1

PATIENT CHARACTERISTICS OF THE HYPOGONADAL SUBJECTS

No.	Age	Diagnosis	Previous Treatment
1	29	Bilateral testicular tumour. Castration age 28.	T.U.
2.	31	Kallman's syndrome.	Testosterone implants HCG, Sustanon
3.+	32	Pituitary tumour. Excision age 22.	Fluoxymesterone
4.++	24	Pituitary tumour. Excision age 17.	Sustanon
5.	26	Klinefelter's syndrome	None
6.	35	Bilateral testicular torsion at age 15 + 16.	Fluoxymesterone
7.+++	40	Gonadal dysgenesis, primary hypergonadotrophic hypogonadism	Sustanon
8.	55	Pituitary tumour. Excision age 53.	Sustanon

\+ Retention of sexual response while in the hypogonadal state, masturbating to orgasm and ejaculation at a frequency greater than once per week.

++ Massively obese.

+++ Complained of feeling unwell for the few days following i.m. testosterone injections (when circulating levels would be at their highest). Similarly affected during blind high dosage T.U. treatment.

administered via rectal suppository) in order to reach the target organs before hepatic degradation, or the molecule must be modified by introducing a methyl group at the carbon 17 position to become orally effective (Neumann et al. 1978). As frequent injections and minor surgery are obviously inconvenient for the patient and practitioner, orally active androgens would appear to be the preferable method of treatment (Davidson et al. 1979). Orally active androgens such as methyltestosterone have been used clinically, but evidence is mounting that carbon 17 alkylated derivatives of testosterone have hepatoxic side-effects (Hirschhauser and Hopkinson, 1974; Coert et al. 1975; Farrell et al. 1975; Leska et al. 1976; Neumann et al. 1978). In reviewing the field, Neumann et al. (1978) state that "all orally active androgens are 17 alkylated derivatives of testosterone. There is therefore a real fear that by administration of these derivatives over longer periods of time, liver damage may occur". Neumann et al. (1978) were not totally accurate making this statement, for recently a non-17 alkylated orally active androgen, Testosterone Undecanoate (T.U.) has been manufactured (Hirschhauser and Hopkinson, 1974; Nieschlag et al. 1975). T.U. is fat soluble and is absorbed via the lymphatic system and the peripheral circulation is reached before inactivation of the steroid by the liver (Kloer et al, 1980).

Experiments carried out on hypogonadal and eugonadal men have shown that T.U. administration results in an increase in plasma androgen concentration after several hours (Hirschhauser and Hopkinson, 1974; Hirschhauser et al. 1975; Nieschlag et al. 1975). Over the last few years T.U. has been used extensively as replacement therapy

for male hypogonadism, with a high degree of reported efficacy. The doses of T.U. that have been used to treat male hypogonadism are shown in Table 3.2.

In none of the studies cited were any hepatoxic effects reported. Franchi et al. (1978) studied liver function and size and consistency of the prostate, and eight months of treatment with T.U. resulted in no change. More recently Gooren et al. (1982) reported that treatment for up to fifty-six months had no adverse effects on the liver function of the patients who were studied.

The evidence accumulated to date indicates that oral T.U. is a safe and acceptable form of androgen therapy. Frequent oral administration of the androgen facilitates better control over the input of testosterone to the systemic circulation of the hypogonadal man, in contrast to the depot loading and uncontrolled release of testosterone which follows intramuscular injection.

3.2.3 Design

The study lasted for five months, i.e. five assessment periods each lasting one month. The first assessment period acted as a baseline, and in the remaining four periods T.U. was administered.

All subjects stopped taking their existing androgen preparations at least four weeks before the start of the study (i.e. each subject was withdrawn from testosterone replacement for at least eight weeks prior to the beginning of T.U. administration within the study).

During the first assessment period basal endocrine and behavioural measures were obtained. A minimum of three blood samples were taken from each subject during the baseline month to confirm the hypogonadal

TABLE 3.2

LITERATURE REVIEW OF T.U. DOSAGES USED IN THE TREATMENT OF MALE HYPOGONADISM

Author	Year	No. of Subjects	Daily Dose (mg/day)
Hirschhauser & Hopkinson	1974	1	60-90
Mies & Krempl	1977	10	160
Sarris et al.	1977	3	120
Franchi et al.	1978	34	40-120
Franchimont et al.	1978	10	120-240
Skarabalo et al.	1978	4	160
Geere et al.	1980	9	40-80
Luisi & Franchi	1980	12	120
Weil et al.	1980	12	40-80
Maisey et al.	1981	69	80-160
Skakkebaek et al.	1981	12	160
Gooren et al.	1982	65	80-160
Salmimies et al.	1982	15	80-200
Wu et al.	1982	4	160

diagnosis. Following the baseline assessment period subjects were administered T.U. for four months. Four of the eight subjects received monthly increments in T.U. replacement, i.e. 40 → 160 mg/day, four

TABLE 3.3 Daily T.U. Dosage per Month

	Month 1	Month 2	Month 3	Month 4	Month 5
N = 4	0	40mg	80mg	120mg	160mg
N = 4	0	160mg	120mg	80mg	40mg

received successive monthly decrements, from 160 → 40 mg/day, as shown in Table 3.3. Throughout the four months of T.U. administration bloods were taken twice a day at 0900 and 1300 hours at fortnightly intervals, that is prior to, and four hours after ingestion of the morning dose of T.U. (as previously described by Skakkebaek et al. 1981). For the four months of T.U. administration each subject took two capsules at 0900 hrs and two at 1700 hrs, as shown in Table 3.4. Using this methodology subjects were blind as to their replacement dosage, as all subjects took four identical capsules per day for the four months of T.U. administration.

TABLE 3.4 Daily T.U. Dosage Scheme		
T.U. Dose	0900 hrs	1700 hrs
40 mg/day	1 40mg capsule 1 placebo capsule	2 placebo capsules
80 mg/day	1 40mg capsule 1 placebo capsule	1 40mg capsule 1 placebo capsule
120 mg/day	2 40mg capsules	1 40mg capsule 1 placebo capsule
160 mg/day y	2 40mg capsules	2 40mg capsules

The design was double-blind and the dosage regimes were allocated to subjects arbitrarily. This methodological design is an improvement on that used by Salmimies et al. (1982) who stated "A double-blind design was not used for several reasons. A double-blind study would have required an alteration in the sequence of treatment periods. However, it is difficult to study a low dose after a period with a high testosterone dose because overlap can occur". The experimental design developed for the present study, i.e. gradual increments or decrements in replacement dose would appear to overcome these difficulties. The range of T.U. dosage regimes was selected as being representative of the doses that have been reported in the literature for the treatment of male hypogonadism (see Table 3.2).

3.2.3.1 Endocrine Assessment

Following venepuncture blood samples were centrifuged and plasma stored at -20°C. All samples were measured for testosterone in a single assay using the method described by Corker and Davidson (1978).

3.2.3.2 Behavioural Assessment

All subjects completed a coded daily diary form for the duration of the study (Appendix IV). On this form subjects reported presence or absence of erections on waking, occurrence, description and qualitative rating of sexual activity, whether the activity was self, partner or jointly initiated, and whether or not ejaculation resulted. Subjects also rated themselves for frequency of sexual thoughts and sexual excitement accompanying these thoughts on two separate 100mm visual analogue scales. Mood state was also recorded daily. (Subjects completed the daily diary form for four weeks before entering the study proper. This allowed subjects to become accumstomed to completing the diary form on a daily basis. During this period the author checked the forms and advised individuals who were unsure as to what was required. This "practice" data was not included in the final analysis).

3.2.4 Analysis

In order to allow direct comparison with the very similar study of Salmimies et al. (1982), exactly the same form of statistical analysis was employed, i.e. comparing each subject's monthly treatment mean behavioural rating against his mean basal levels, using Wilcoxon's test for paired data. All visual analogue data was standardised using the method described in Chapter 2.1.1, i.e. each man's monthly mean visual analogue scores were expressed as deviations from his overall mean

score for the five month study period. These deviations were then standardised using the proportional method and were expressed as a percentage of the range of the scale used by that individual over the five months.

The effect of T.U. ingestion on circulating testosterone levels was assessed using the paired t-test (a.m. versus p.m. values). Complete endocrine data was available for only seven out of the eight subjects, as subject no.1 was unable to attend for all of the blood sampling due to work commitments.

3.3 RESULTS

The results of the effects of varying the replacement dosage of T.U. on circulating testosterone levels, sexual behaviour and mood state are displayed in Figs. 3.1 - 3.10.

Oral ingestion of T.U. resulted in marked elevations in plasma testosterone levels (although at the highest dose, 160 mg/day, this increase did not reach statistical significance).

The behavioural data is summarised in Figs. 3.2 - 3.10. The mean score represents the standardised mean visual analogue score for the whole group over the entire study period. The behavioural effects of varying the replacement dose of T.U. are expressed as percentage deviations from this overall group mean.

Dose response relationships between T.U. replacement and sexual behaviour were demonstrated most clearly for frequency of sexual thoughts, arousal accompanying these thoughts, and frequency of reported erections on waking. The hypogonadal men also rated themselves as feeling less tense and anxious, changeable, and irritable while taking the higher doses of T.U. as compared with no treatment.

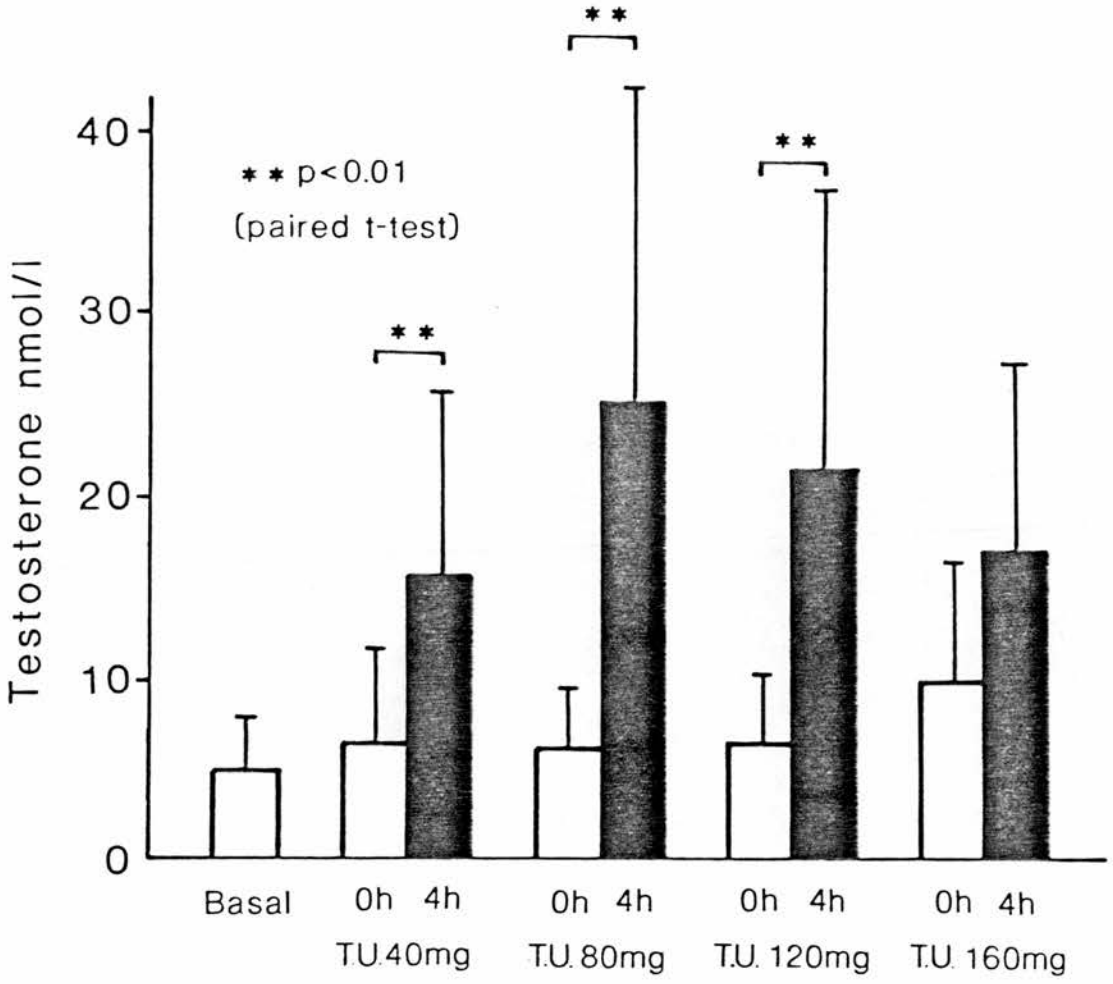

FIGURE 3.1

The effect of varying the replacement dose of T.U. on mean circulating testosterone levels in seven hypogonadal men.

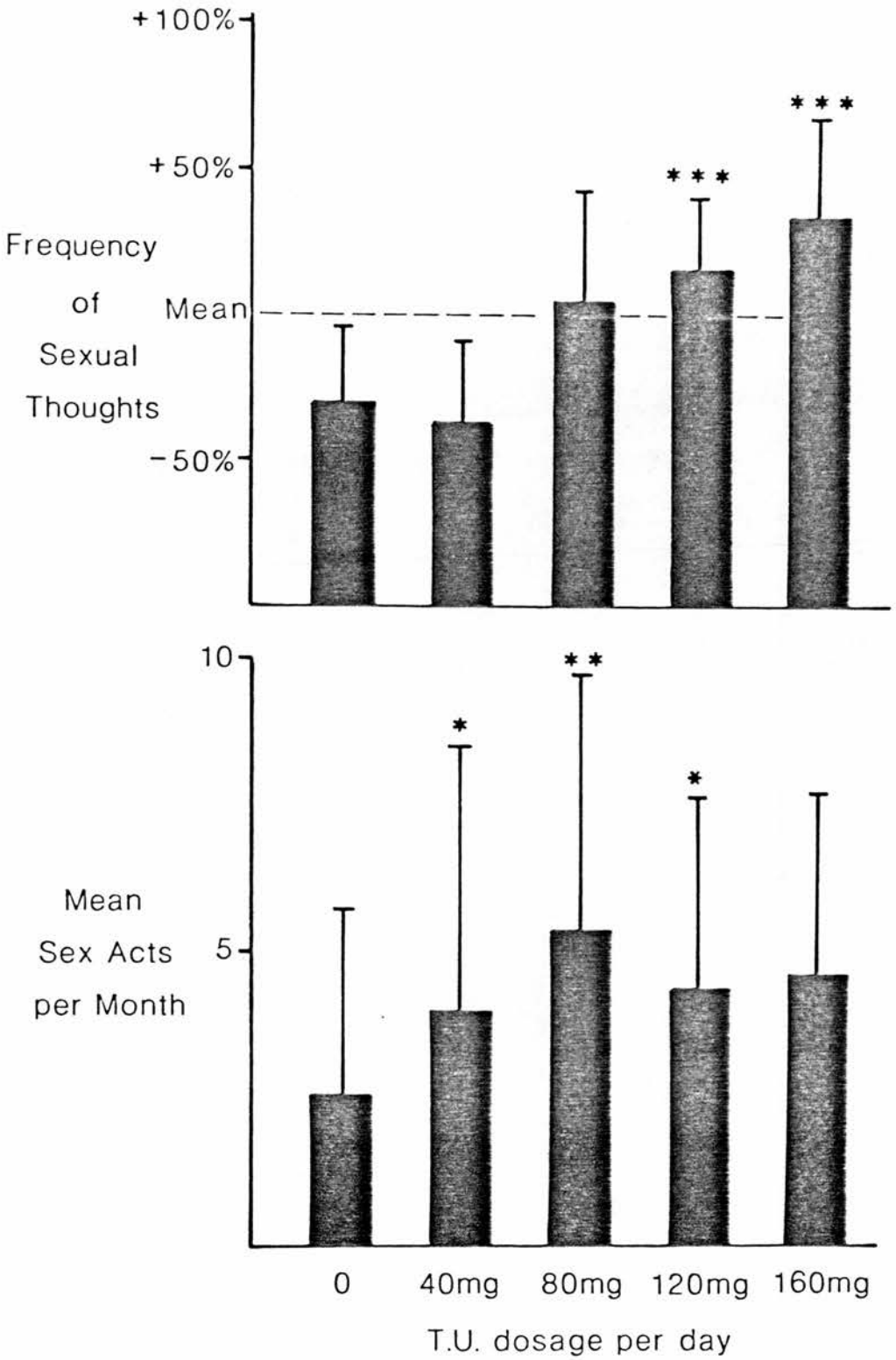

FIGURE 3.2

The effect of varying the replacement dose of T.U. on mean frequency of sexual thoughts and mean sex acts per month in eight hypogonadal men.

*p<0.05, **p<0.025, ***p<0.01 in comparison with no treatment (one tailed Wilcoxon test).

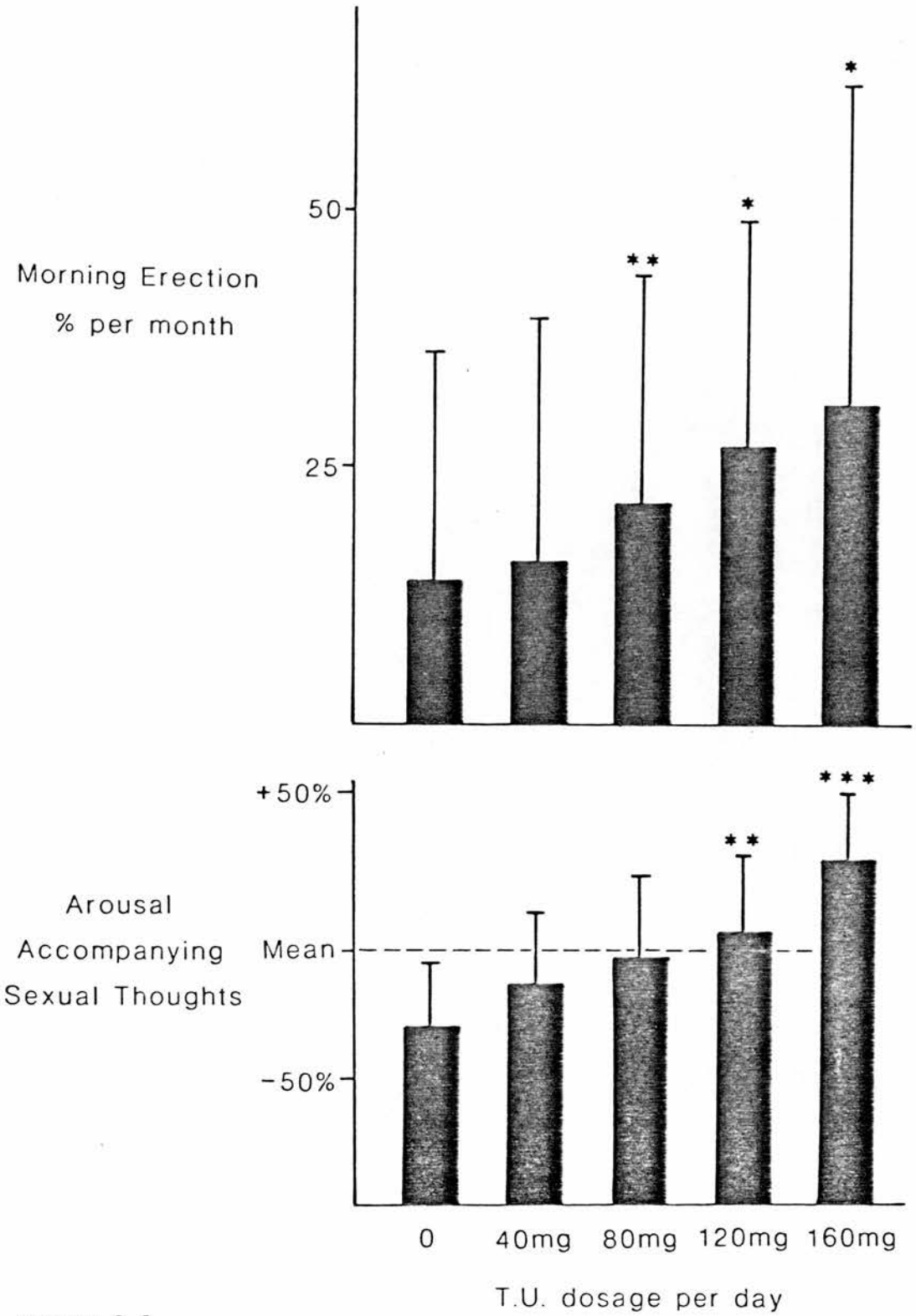

FIGURE 3.3

The effect of varying the replacement dose of T.U. on mean frequency of morning erections and self-rated arousal accompanying sexual thoughts in eight hypogonadal men.

*p<0.05, **p<0.025, ***p<0.01 in comparison with no treatment (one tailed Wilcoxon test).

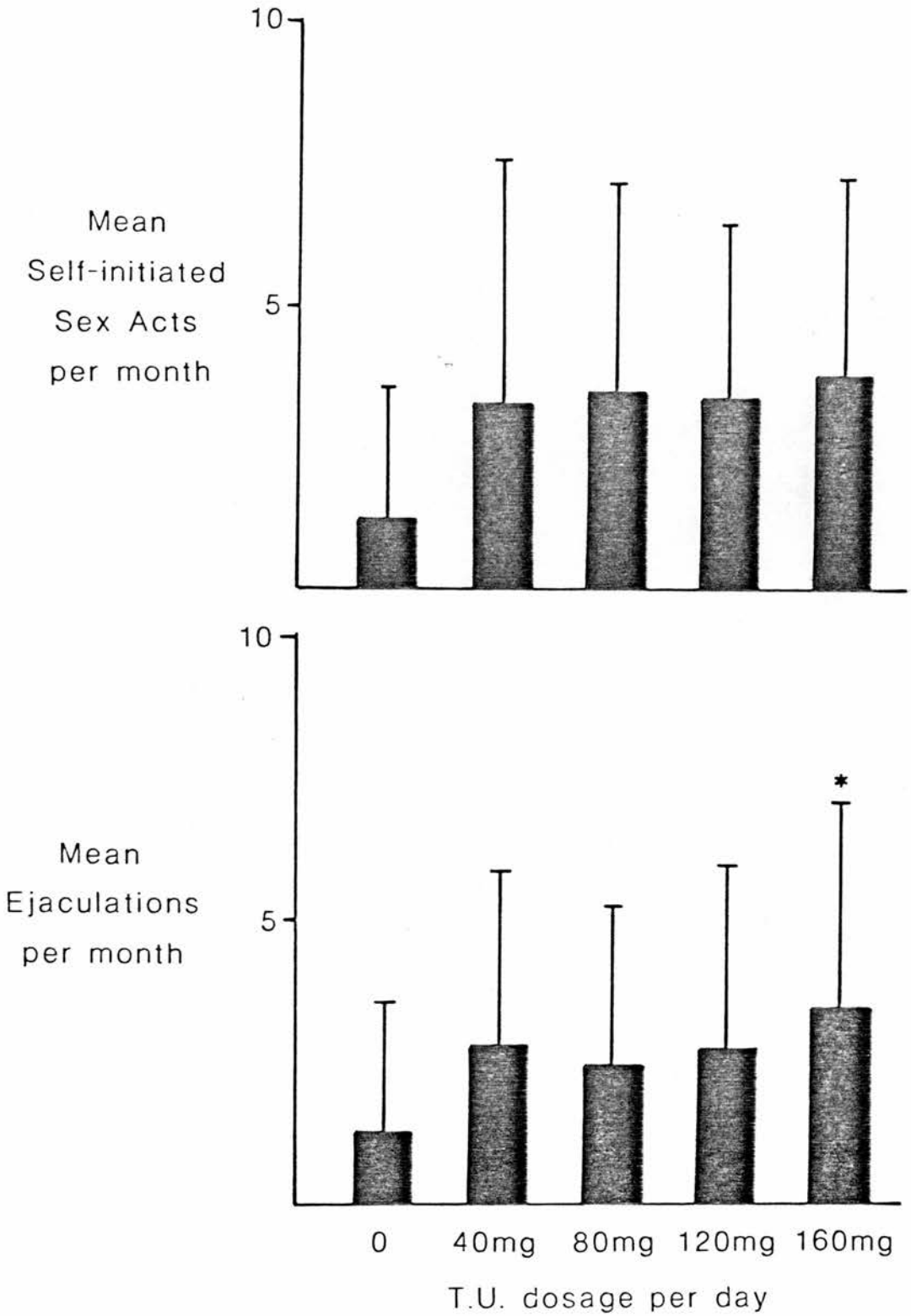

FIGURE 3.4

The effect of varying the replacement dose of T.U. on mean frequency of self-initiated sex acts per month and mean ejaculation frequency per month in eight hypogonadal men.

*$p<0.05$ in comparison with no treatment (one tailed Wilcoxon test).

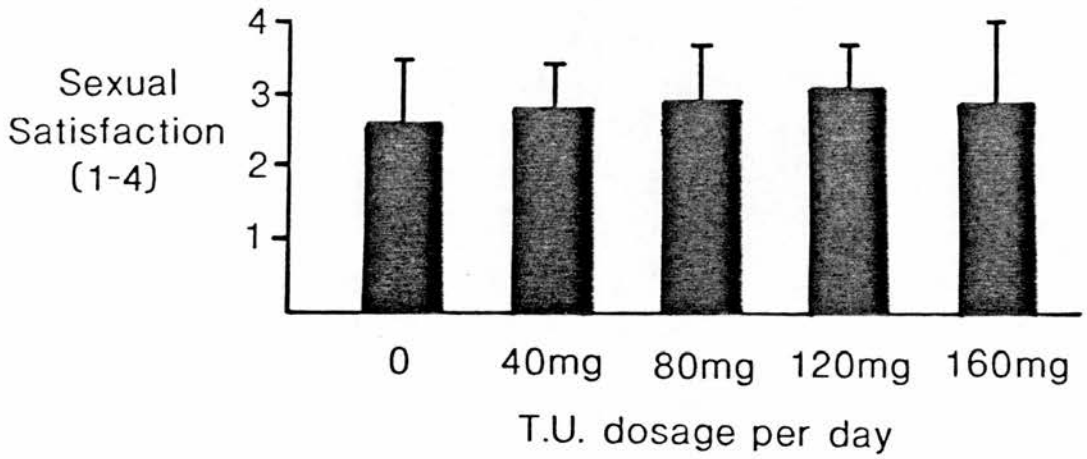

FIGURE 3.5

The effect of varying the replacement dose of T.U. on mean self-rated sexual satisfaction per month in eight hypogonadal men. All comparisons with no treatment non-significant (one tailed Wilcoxon test).

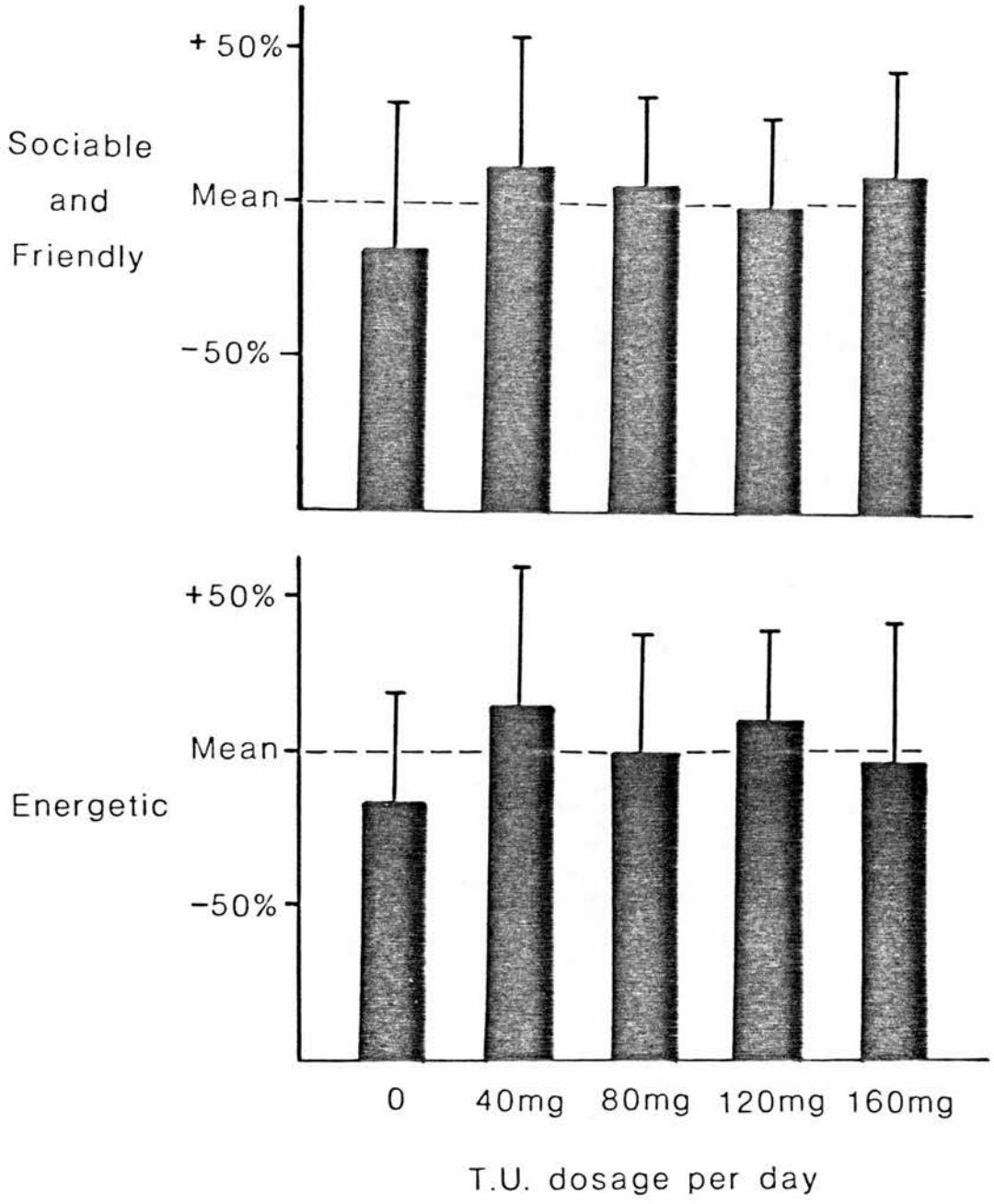

FIGURE 3.6

The effect of varying the replacement dose of T.U. on self-rated mood states "Sociable and Friendly" and "Energetic" in eight hypogonadal men. All comparisons with no treatment non-significant (two tailed Wilcoxon test).

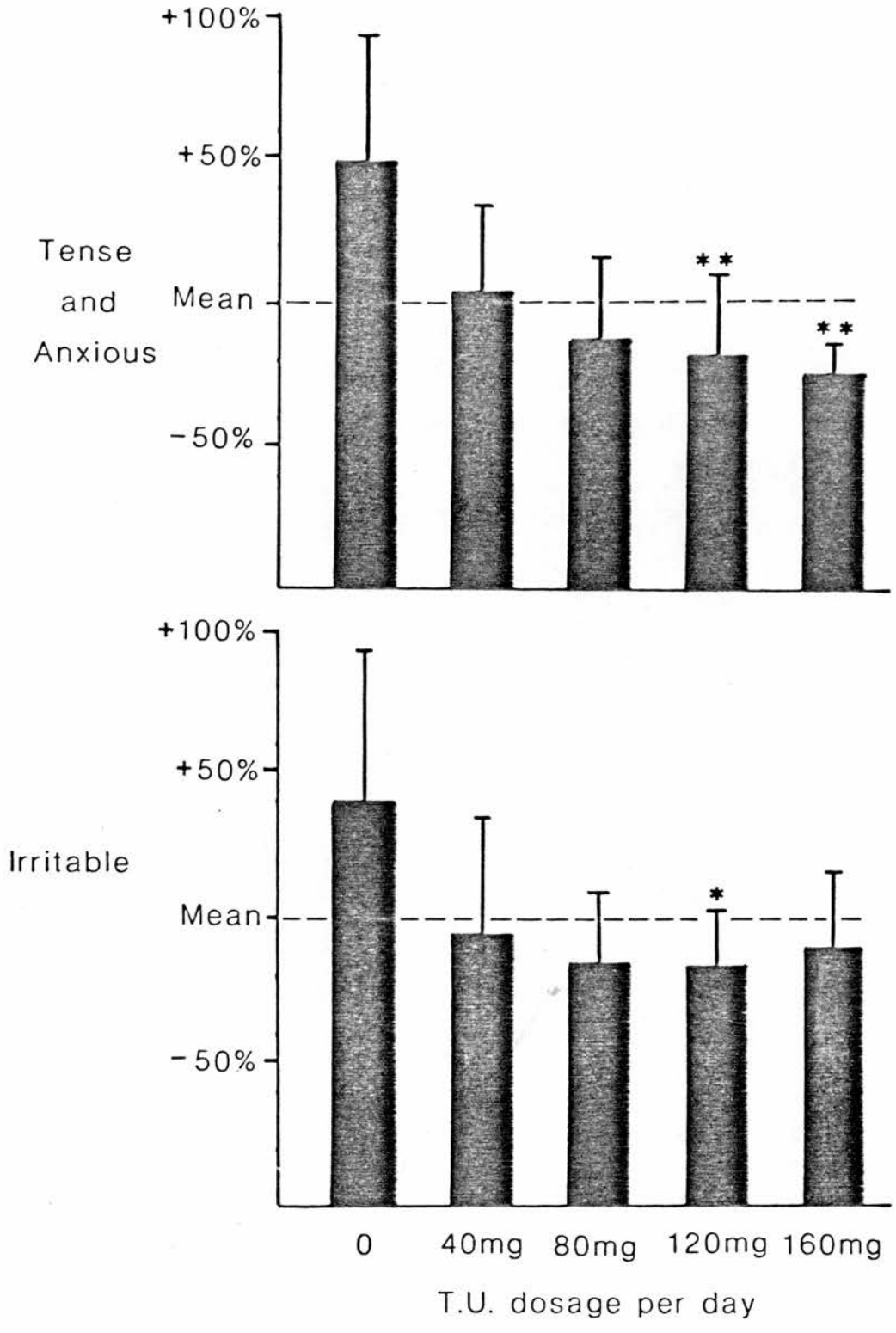

FIGURE 3.7

The effect of varying the replacement dose of T.U. on self-rated mood states "Tense and Anxious" and "Irritable" in eight hypogonadal men.

*p<0.05, **p<0.02 in comparison with no treatment (two tailed Wilcoxon test).

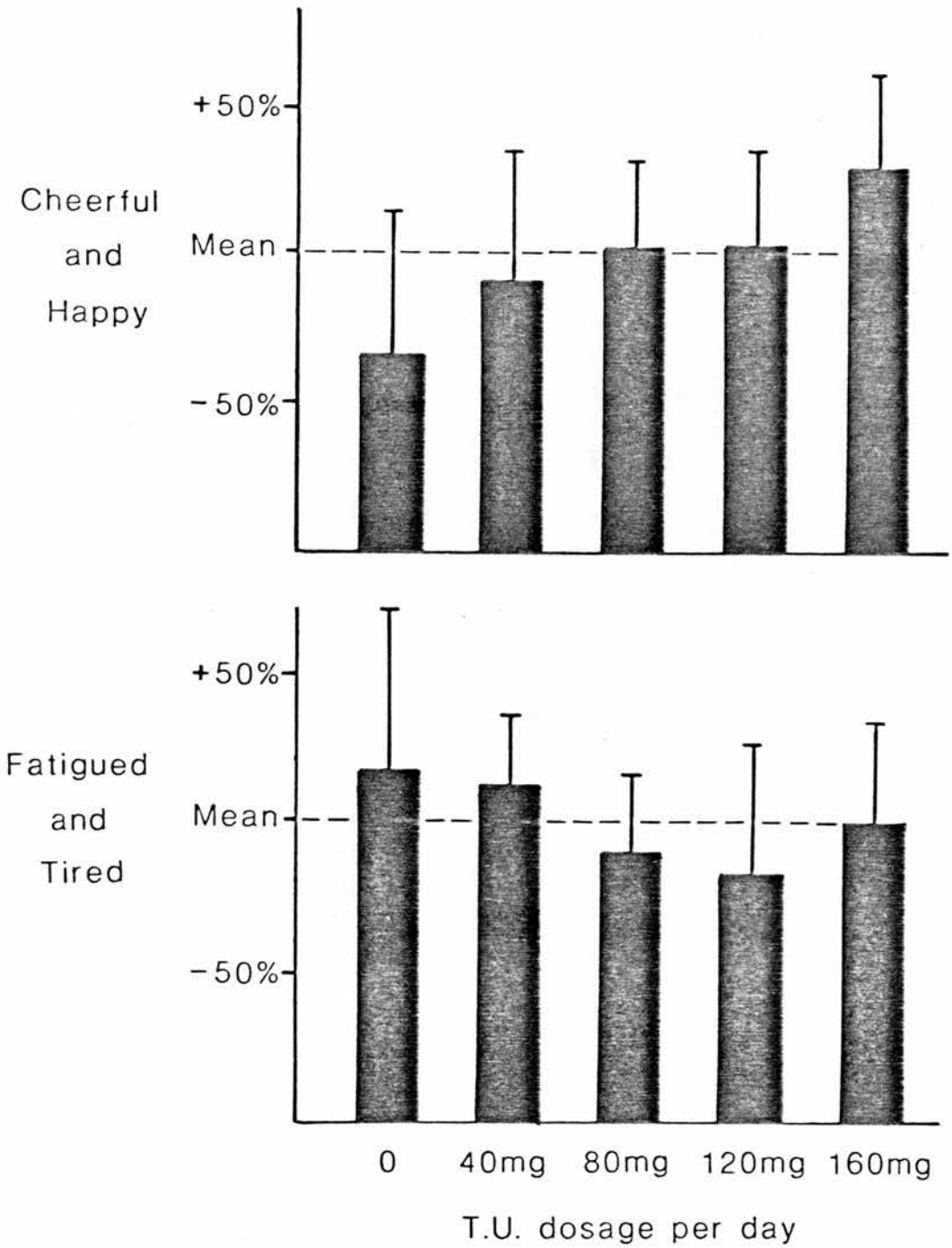

FIGURE 3.8

The effect of varying the replacement dose of T.U. on self-rated mood states "Cheerful and Happy" and "Fatigued and Tired" in eight hypogonadal men. All comparisons with no treatment non-significant (two tailed Wilcoxon test).

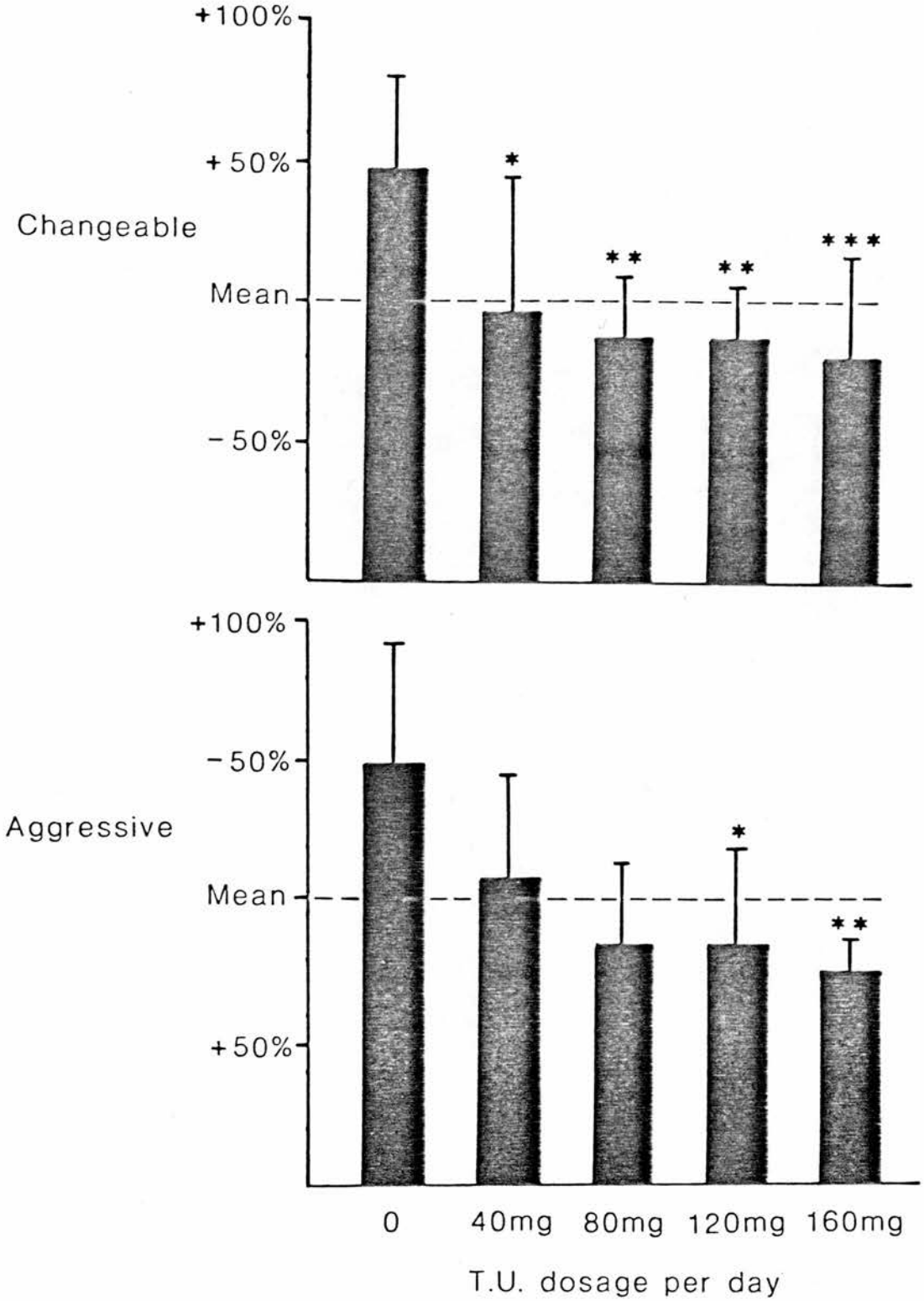

FIGURE 3.9

The effect of varying the replacement dose of T.U. on self-rated mood states "Changeable or Up and Down" and "Aggressive" in eight hypogonadal men.

*p<0.05, **p<0.02, ***p<0.01 (two tailed Wilcoxon test).

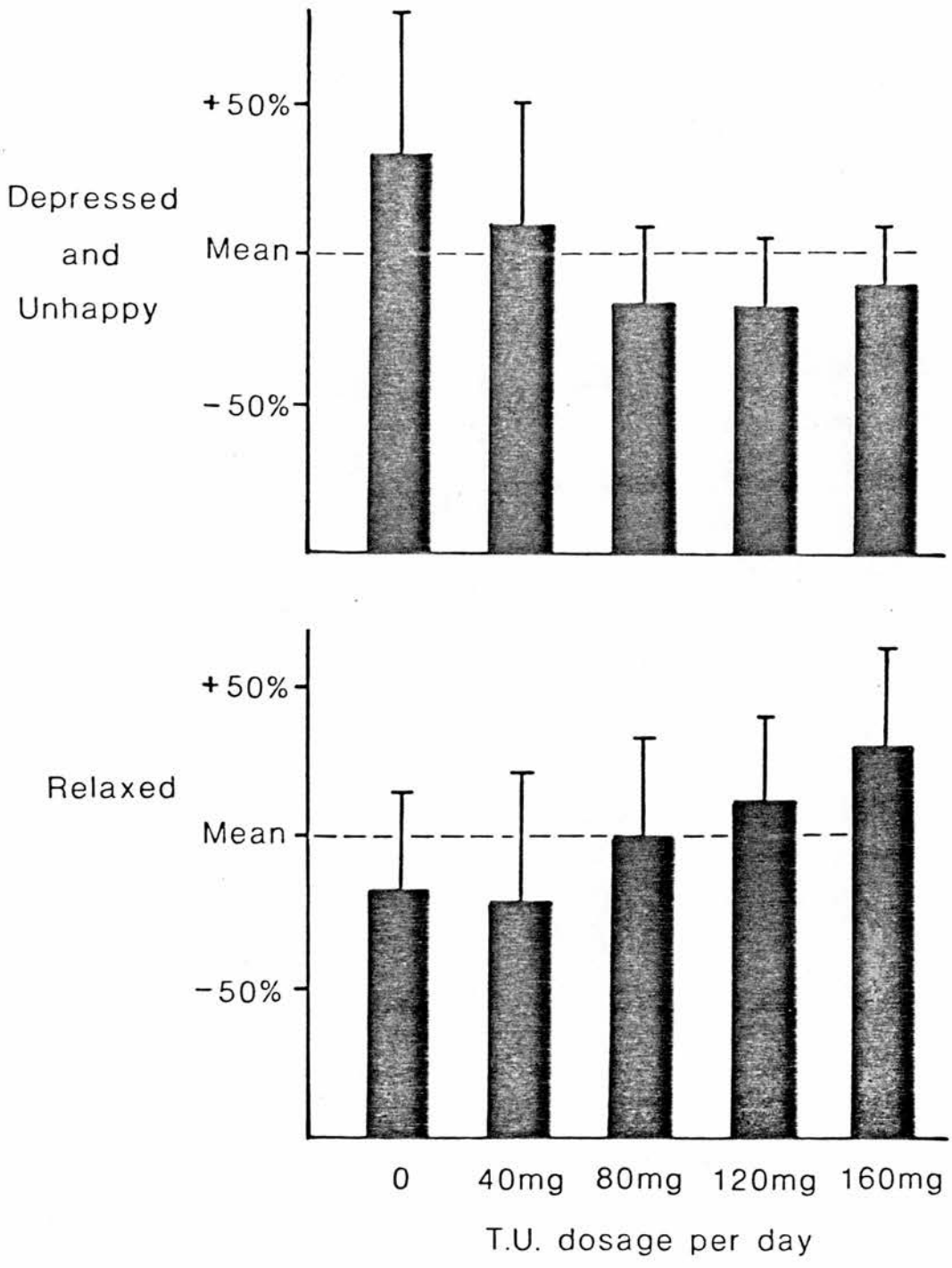

FIGURE 3.10

The effect of varying the replacement dose of T.U. on self-rated mood states "Depressed and Unhappy" and "Relaxed" in eight hypogonadal men. All comparisons with no treatment non-significant (two tailed Wilcoxon test).

3.4 DISCUSSION

3.4.1 Testosterone Levels

Administration of T.U. acted to increase circulating testosterone levels. However a linear incremental increase in systemic testosterone level with increasing dosage of T.U. was not observed (Fig. 3.1). This may be due to the limitations of our single post-dose blood sampling regime, and could be accounted for by the recent findings that hypogonadal men display a marked degree of intra- and inter-individual variation in the rate at which testosterone blood levels peak following T.U. administration (Cantrill et al. 1983; Schurmeyer et al. 1983). Using a more frequent blood sampling regime, a clearer relationship between testosterone input and circulating testosterone levels may have been observed.

During all dose regimens the post-dose testosterone level was higher than the pre-dose level. Interestingly, at the highest dose of T.U. (160 mg/day) this difference did not reach statisticial significance. This is probably due, in part, to the elevation in the pre-dose (0900 hr) circulating testosterone level, as a result of the high dosage androgen administration.

3.4.2 Sexual Behaviour

The effects of varying the replacement dosage of T.U. on sexual behaviours are exhibited in Figs. 3.2 - 3.5, and in general are very similar to the findings of Salmimies et al. (1982).

Frequency of sexual thoughts when compared with basal values were significantly elevated during the 120 and 160 mg T.U./day dosage regimes. Similar results were observed for the self-rating scale

measuring arousal accompanying sexual thoughts. Ejaculation frequency was significantly raised compared with basal values only during the 160 mg/day period, perhaps indicating that this facet of sexual functioning requires prolonged and high dosage androgen replacement in order to produce marked effects (Skakkebaek et al. 1981). All subjects reported that ejaculation was associated with orgasm on all occasions during the study period. Several men reported an increase in ejaculate volume throughout the study.

The mean frequency of sexual acts, while higher on T.U. than on no treatment, did not appear to vary in a dose-dependent manner. This may be because androgens act primarily on sexual interest (Bancroft, 1980), and this is not reflected in the gross measure of the sexual activity of the dyad. The findings of the present study suggest that sexual interest (as reflected by self-rated sexual thoughts) varies in a dose-dependent manner with androgen replacement, thus supporting the Bancroft (1980) hypothesis. One would then perhaps expect this androgen effect on sexual appetite to be reflected in the frequency of self-initiated sexual acts; however, this effect was not observed.

It is also of interest to note that while Bancroft (1980) suggested that erectile function per se is not affected by androgen status, the present study confirms Davidson et als' (1979) finding, i.e. morning erections in the hypogonadal man vary in a dose-dependent manner with androgen replacement (Fig. 3.3). This finding has to be viewed in light of the recent report by Bancroft and Wu (1983) who claimed that erections in response to erotic film were not affected by androgen replacement or withdrawal, whereas erections in response to

erotic fantasy were markedly affected. It may be that erections on waking (i.e. residual nocturnal erections) are qualitatively different from conscious erections in response to erotic film, e.g. erections on waking may be similar to the fantasy erections of the Rancroft and Wu (1983) study in that the stimulus for the erection is generated internally as opposed to the external film stimulus. (The effect of androgen replacement on nocturnal erections is discussed in detail in Chapter 7). However, it is also important to note that Kwan et al. (1983) have recently failed to replicate Rancroft and Wu's (1983) finding by reporting that erections in response to erotic film and fantasy were both unaffected by testosterone withdrawal and replacement.

Davidson et al. (1982) hypothesised that androgens mediate their behavioural effect by increasing the subjective pleasurable awareness of sexual response. This was tested in the present study by comparing self-rated sexual satisfaction across treatment periods (Figure 3.5) and no significant differences were observed. However, it is difficult to make firm conclusions regarding the Davidson et al (1982) hypothesis from this small experiment, the major problem being that sexual activity is such a rare occurrence in the untreated hypogonadal man. However, one subject in the present study (no.3) did display a masturbation and ejaculation frequency of greater than once per week while markedly hypogonadal (mean testosterone level, 6.6 nmol/l). Salmimies et al. (1982) similarly reported that four of their fifteen subjects also reported a marked degree of sexual activity while in the hypogonadal state.

In conclusion, dose-response relationships between androgen replacement and sexual behaviour were demonstrated most clearly for self-rated frequency of sexual thoughts, associated arousal and erections on waking.

3.4.3 Mood

In general, the effects of T.U. administration on self-rated mood are very simlar to those observed by Skakkebaek et al. (1981) who, using the Lorr-McNair MACL, reported that anxiety and tension, anger and fatigue were decreased and vigour increased following T.U. administration as compared with placebo. In the present study the hypogonadal subjects rated themselves as feeling less tense and anxious, changeable and irritable while taking the higher doses of T.U. as compared with no treatment. It is also extremely interesting to note that the hypogonadal men rated themselves as feeling less aggressive while taking the higher doses of T.U. (The relationship between androgens and aggression in man is discussed in detail in Chapter 9).

The design of the present study does not enable us to directly test the hypothesis proposed by Kinsey et al. (1953), i.e. that androgens act primarily on general metabolism and mood and only secondarily on sexual behaviour. However, as the general effect of T.U. treatment on mood state was modest (e.g. no effect on six out of the ten mood scales) and not closely related to androgen replacement dose, it is possible that the mood changes rather than causing the improvement in sexual behaviour were in fact a result of the general improvement in sexual functioning. Anxiety and general negative mood

states may have been partially due to the sexual difficulties associated with hypogonadism and would thus tend to improve following the beneficial effects of androgen replacement on sexual functioning. The Kinsey et al (1953) hypothesis appears even less convincing when one considers that Davidson et al. (1979) and Salmimies et al. (1982) both reported no effect of testosterone administration on mood, yet found clear beneficial effects of androgen replacement on sexual functioning in the hypogonadal man.

CHAPTER 4

ANDROGEN ADMINISTRATION TO EUGONADAL MEN - THE DIFFICULTIES IN RAISING CIRCULATING ANDROGEN LEVELS

4.1 INTRODUCTION

Androgen replacement is generally considered to be unhelpful in the treatment of sexual dysfunction in men with normal circulating levels of testosterone (Cooper et al., 1973; Benkert et al., 1979). Hypogonadal men, on the other hand, show definite improvements in sexual interest and function with androgen replacement (Davidson et al., 1979; Skakkebaek et al., 1981). The usual explanation given is that a certain amount of androgens are required for sexual response and any increase above this level will have no additional effect (Pirke & Kockott, 1982). A further explanation deserves consideration; the normal homeostatic mechanisms (LH suppression with consequent reduction in endogenous testosterone production and sex hormone binding globulin (SHBG) reduction leading to increased metabolic clearance) make it difficult to raise circulating testosterone levels in eugonadal men. In the studies of eugonadal men receiving androgens for sexual dysfunction circulating testosterone levels have either not been measured (Jakobovitz, 1970) or have shown no increase with treatment (Benkert et al., 1979). If it were possible to sustain a substantial increase, behavioural effects might be produced even with increases within the normal range.

Two types of testosterone administration are now in general use; testosterone undecanoate administered orally and intramuscular injections of testosterone esters (e.g. Sustanon or testosterone oenanthate).

Testosterone undecanoate (T.U.) is largely absorbed by the lymphatics, and so far hepatoxic effects have not been observed even after long-term administration (Franchi et al., 1978; Gooren et al., 1982). It has been shown to be a very satisfactory form of androgen

replacement in hypogonadism (Franchi et al., 1978; Franchimont et al., 1978; Skakkebaek et al., 1981; Maisey et al, 1981). In normal men, single dose administration leads to a significant increase in circulating testosterone levels, reaching a maximum approximately 4-5 hours after oral ingestion (Nieschlag et al., 1975). However with more prolonged administration, especially of high doses, the plasma testosterone concentration may be suppressed (Benkert et al., 1979; Nieschlag et al., 1978). In studies of hypogonadal men, testosterone undecanoate produces an increase in circulating DHT which is relatively greater and more sustained than the rise in testosterone (Franchimont et al., 1978; Skakkebaek et al., 1981; Wu et al., 1982).

The pharmacodynamics of injected testosterone esters in eugonadal men have mainly been studied in the case of testosterone oenanthate, cypionate and propionate (Nieschlag et al., 1976; Steinberger, 1980; Schulte-Beerbuhl & Nieschlag, 1980 and Sokol et al., 1982). In most cases plasma testosterone levels were maximal for one to two days and remained elevated for seven to ten days following each injection. Plasma DHT was found to be raised after testosterone oenanthate for about 5 days (Schulte-Beerbuhl & Nieschlag, 1980).

In this study we have compared three different dosages of testosterone undecanoate as well as Sustanon 250 injection (a mixture of 4 esters, propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg and decanoate 100 mg) in normal men with particular reference to the total and free testosterone, DHT, SHBG and LH levels in the plasma. The purpose of this study is to establish the best regime for producing maintained elevation of plasma testosterone in eugonadal men, in order

to investigate the behavioural effects of this endocrine manipulation in eugonadal men complaining of sexual dysfunction.

4.2 MATERIALS AND METHODS

4.2.1 Subjects

Eight normal men (age 20-44 years, mean 34.1 years) were recruited from hospital and Unit staff. Each was shown to have normal liver function tests and plasma acid phosphatase levels before inclusion in the study.

4.2.2 Design

The study period lasted for 10 weeks, during which time blood samples were taken at 0900 hrs and 1300 hrs on two days per week. By taking samples before the morning dose, at 0900 hrs and four hours later, we aimed to measure the "peak" and "trough" in daily T levels and arrive at a representative mean T level for the day.

The 8 men had blood samples taken for one week to determine baseline values and were then randomly allocated into two groups A and B, four men in each. Group A had two 3 week periods of T.U. administration separated by a 3 week interval (to act as a washout phase). The two dose regimes were 80 mg per day and 160 mg per day and the order of presentation of these two regimes was balanced. The T.U. capsules (40 mg each) were taken at 0900 hrs and at 1700 hrs. The design for group B was exactly the same except the comparison was between a single injection of Sustanon 250 and T.U. at a dosage of 240 mg per day (taken in 80 mg doses at 0900 hrs, 1300 hrs and 1700 hrs). Subjects receiving the Sustanon had additional blood samples taken the day after injection.

4.2.2.1 Hormone Measurement

Total testosterone was assayed using the method described by Corker & Davidson (1978). A ratio of free to total testosterone was measured according to the method of Bergink et al. (1981); concentration of free testosterone was then estimated by applying this ratio to the total testosterone concentration. SHBG was measured according to Anderson et al. (1976) and LH according to Hunter & Bennie (1979). DHT was assayed only in group B, after chromatography on celite columns using a modification of the method of Thorneycroft et al. (1973).

4.2.3 Analysis

Mean differences in hormone levels were assessed using analysis of variance for repeated measures and the Scheffé method to compare differences between treatments. Due to the highly skewed distribution of plasma concentrations following Sustanon administration, log transformation of the data was used for group B.

4.3 RESULTS

Mean levels for total testosterone, estimated free testosterone, SHBG and LH for the baseline week and each 3 week period are shown for Group A in Table 4.1 and for group B in Table 4.2 (together with plasma DHT levels).

In group A there were no significant differences between either dose regime and baseline or interval levels in any of the hormones measured, though total and estimated free testosterone were higher and SHBG and LH levels lower during the high dose administration.

In group B, differences were more marked. The higher mean levels of testosterone during Sustanon administration were mainly due to very high levels within the first few days (see Fig. 4.1). With log transformation the differences between periods did not reach statistical significance. Both T.U. 240 mg per day and Sustanon produced significant lowering of SHBG compared with baseline levels*. In addition, SHBG remained significantly depressed during the interval washout period, presumably due to carry over suppression following the first androgen administration.

Although LH levels were lower during Sustanon and T.U. administration, the differences were not significant when compared with basal values. DHT levels were significantly greater during T.U. 240 mg per day administration compared with both baseline ($p = < 0.01$) and Sustanon administration ($p = < 0.01$).

In group B changes in the SHBG levels and ratio of free to total testosterone were looked at week by week (see Figs 4.2 and 4.3). Following Sustanon injection, the percentage of free testosterone was maximal in the first week and thereafter progressively fell. Reciprocally the SHBG levels were lowest during the first week followed by a progressive rise. Comparison of levels the day after the Sustanon inejction with baseline showed an approximately 400% increase in total testosterone concentration (Fig. 4.1). During administration of

*The degree of reduction in SHBG levels following T.U. administration observed in this study may have been slightly over-estimated as a result of the assay method used to determine SHBG binding capacity (See Appendix II).

TABLE 4.1

EFFECTS OF TESTOSTERONE ADMINISTRATION ON PLASMA CONCENTRATIONS OF HORMONE AND BINDING CAPACITY - MEANS (± S.D.) IN GROUP A

Plasma Hormone Concentration	Baseline (1 week)	Interval (3 weeks)	T.U. 80mg/day (3 weeks)	T.U. 160mg/day (3 weeks)	Statistical Comparison
Total Testosterone nmol/l	28.8 (5.0)	28.2 (7.6)	27.4 (6.3)	33.1 (11.4)	N.S.
Estimated Free Testosterone nmol/l	0.91 (0.2)	0.82 (0.2)	0.93 (0.3)	1.14 (0.5)	N.S.
SHBG nmol/l	31.4 (14.1)	30.7 (11.7)	32.7 (11.1)	29.3 (12.4)	N.S.
L.H. mu/ml	7.5 (2.5)	7.3 (3.1)	6.5 (2.5)	5.9 (2.9)	N.S.

TABLE 4.2

EFFECTS OF TESTOSTERONE ADMINISTRATED ON PLASMA CONCENTRATIONS OF HORMONE AND BINDING CAPACITY - MEANS (± S.D.) IN GROUP B

Plasma Hormone Concentration	Baseline (1 week)	Interval (3 weeks)	T.U. 240mg/day (3 weeks)	Sustanon 250 (3 weeks)	Statistical Comparison
Total Testosterone nmol/l	29.5 (10.5)	26.2 (9.7)	30.5 (17.6)	50.3 (37.8)	N.S. (after log transformation)
Estimated Free Testosterone nmol/l	0.87 (0.3)	0.76 (0.3)	0.98 (0.6)	1.72 (1.5)	N.S. (after log transformation)
DHT nmol/l	1.61 (0.8)	1.64 (0.9)	3.77 (2.4)	2.38 (1.2)	TU v Sustanon p=<0.01 TU v Baseline p=<0.01
SHBG nmol/l	33.3 (4.3)	28.9 (4.2)	27.0 (5.4)	27.7 (4.9)	TU v Baseline p=<0.01 Sustanon v Baseline p=<0.01 Interval v Baseline p=<0.05
L.H. mu/ml	5.4 (1.3)	6.9 (3.5)	4.6 (2.5)	3.9 (2.7)	N.S.

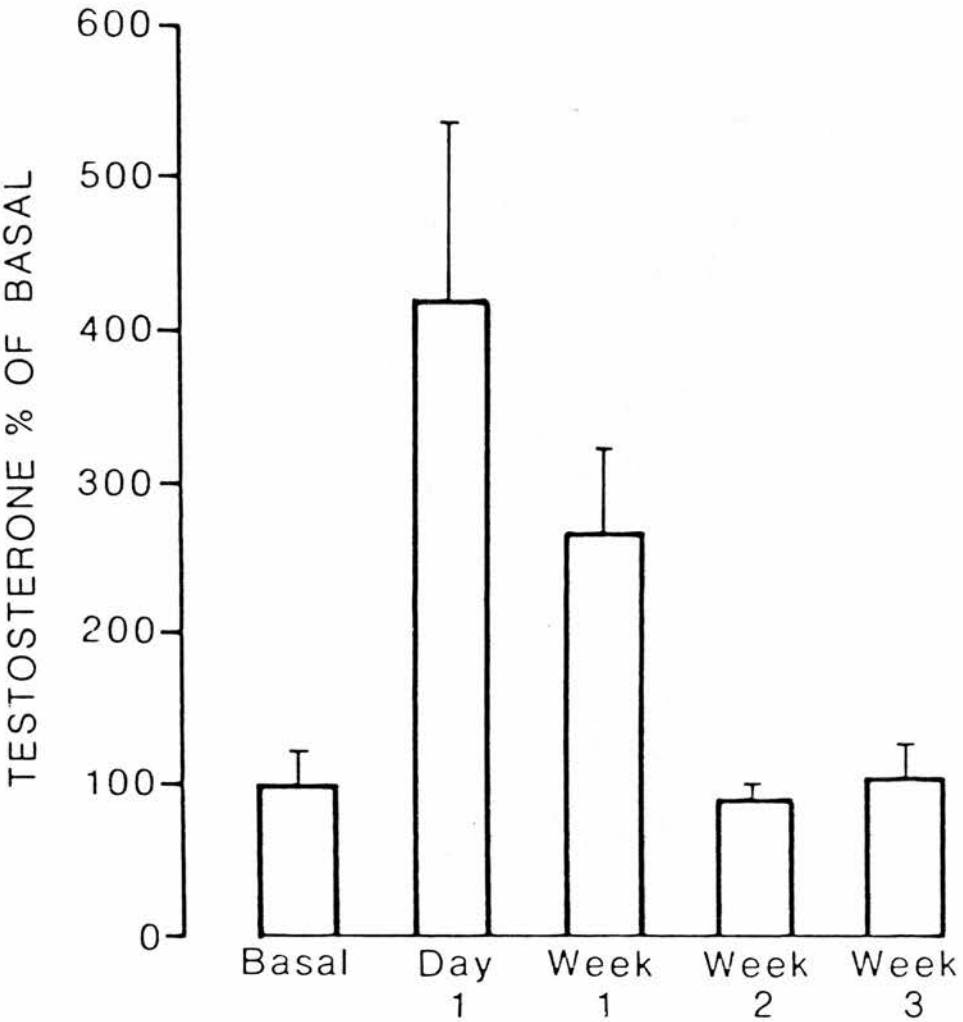

FIGURE 4.1

Effect of a single Sustanon 250 injection on total testosterone levels in 4 eugonadal men.

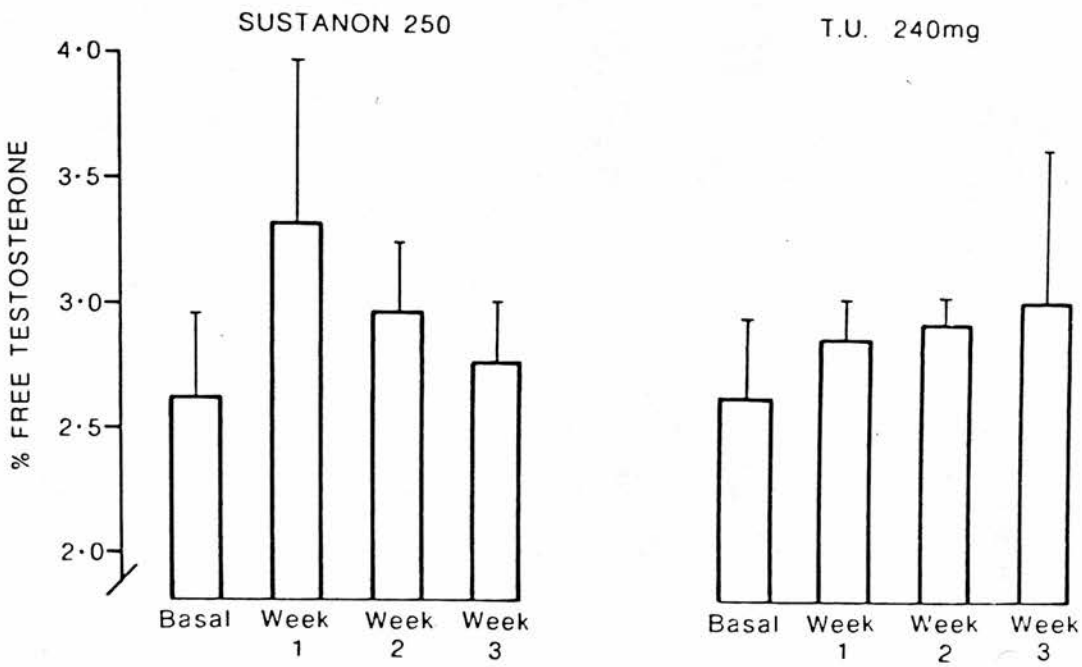

FIGURE 4.2

Percentage unbound (free) testosterone during administration of Sustanon 250 and T.U. 240 mg/day.

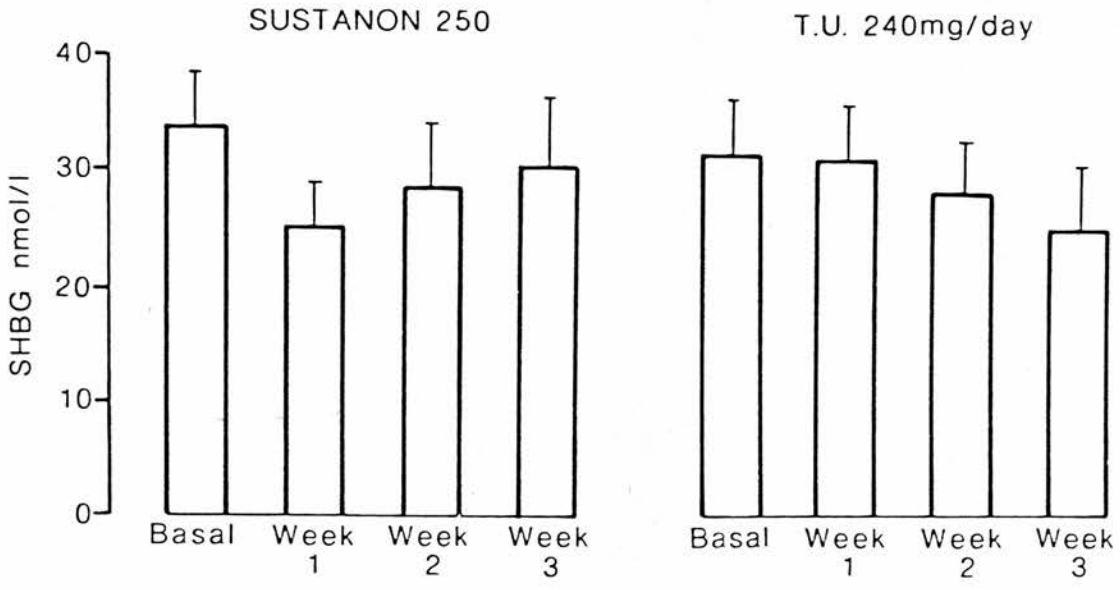

FIGURE 4.3

SHBG levels during administration of Sustanon 250 and T.U. 240 mg/day.

240 mg of T.U. the pattern was quite different. SHBG was progressively falling and the ratio of tree to total testosterone rising during the 3 weeks.

A further difference in the kinetics of the two types of administration is to be expected in the variations during each day. Intermittent oral administration will produce periodic rises reaching a peak several hours after each oral dose. We therefore compared the 0900 hrs (pre-dose) and 1300 hrs (4 hrs post-dose) plasma levels during T.U. administration. Normally there is a fall in testosterone during this part of the diurnal cycle (Mansfield et al., 1974). The effect of treatment was assessed by comparing the change scores (1300 hrs minus 0900 hrs) during the no-treatment (interval) period with those during hormone administration. In group A, the mean change scores ($\pm$ .S.D.) for the 3 conditions were -3.5 (5.2), 1.6 (7.6) and 10.1 (10.76) nmol/l for no treatment, 80 mg T.U. and 160 mg T.U. respectively. Using the paired t-test, the change score comparison was significant for 160 mg T.U. ($p = < 0.01$) but not for 80 mg T.U. In group B the change scores were 4.9 (7.3), 4.5 (16.7) and 3.1 (16.7) nmol/l for no-treatment, T.U. 240 mg and Sustanon 250 mg respectively. The differences were not statistically significant in this group.

4.4 DISCUSSION

With the dosage regimes used in this study, no substantial and sustained increases in circulating testosterone (total or free) were achieved and it is clearly not easy to overcome the homeostatic mechanisms in eugonadal men to produce such an increase. With Sustanon

substantial increases were confined to the first week and when the whole 3 weeks period was taken, and hormone concentrations log transformed to correct the skewed distribution, no significant difference from baseline was found. Injection of Sustanon 250 mg every 7 to 14 days would probably be more effective. A frequency of 10 to 14 days has been suggested for testosterone oenanthate or cypionate (Nieschlag et al., 1976; Schulte-Peerbuhl & Nieschlag, 1980; Sokol et al., 1982). As yet no reports have been published of the kinetics of using such frequent parenteral administration.

For the testosterone undecanoate, the increases in total testosterone were generally very modest. However, progressive increase in the ratio of free to total testosterone shown during administration of T.U. 240 mg daily does raise the possibility that with more prolonged administration a more substantial rise in free testosterone will eventually result.

An alternative explanation for the general lack of effect of T.U. found in this study deserves serious consideration. As stated in the introduction, the post-dose blood sample was taken four hours after ingestion of the T.U. dose. This protocol was chosen in light of the evidence known to the author at the time which suggested that following oral ingestion of T.U., plasma testosterone levels in the eugonadal men reached a maximum after approximately four hours (Nieschlag et al., 1975). However, since the present study was completed, evidence has been presented which suggests that there is in fact a great deal of inter- and intra-individual variation in the rate at which men absorb T.U., with plasma androgens reaching a peak anything from one to eight

hours following ingestion (Cantrill et al., 1983; Schurmeyer et al., 1983). Therefore it is possible that because of the limited single post-dose blood sampling regime used in the present study, the absorption peaks in plasma testosterone levels may not have been picked up. (This variability in the rate of absorption of T.U. was confirmed by the author in a small additional study, summarised in Appendix III).

In the meantime, we must conclude that oral administration of testosterone undecanoate may offer particular advantages in the treatment of male hypogonadism, whereas frequent injection of testosterone esters such as Sustanon would appear to be the best method of producing substantial increases in circulating testosterone levels in eugonadal men.

CHAPTER 5

A CONTROLLED EVALUATION OF TESTOSTERONE TREATMENT IN MEN WITH REDUCED SEXUAL INTEREST

5.1 INTRODUCTION

Clinical impressions concerning the results of androgen replacement therapy in the treatment of hypogonadism led pioneers in the field such as Money (1961) to conclude that "The level of sex drive or libido is hormonally influenced and androgen is probably the libido hormone in both men and women". However it is only in the last four years that methodologically acceptable controlled experiments with hypogonadal men have confirmed the hypothesis that testosterone is directly related to sexual interest and activity in men (Davidson et al. 1979; Luisi and Franchi, 1980; Skakkebaek et al. 1981).

In the eugonadal man, however, correlational studies have suggested that a simple relationship does not exist between circulating total testosterone levels and degree of interest in sex (Monti et al. 1977; Brown et al. 1978) or between circulating testosterone levels and frequency of sexual activity (Raboch and Starka, 1972; 1973; Doering et al. 1974), although positive (Reinberg and Lagoguey, 1978; Tsitouras et al. 1982) and negative relationships (Kraemer et al. 1976) have been suggested.

Most previous studies have concluded that "impotence" is not alleviated by exogenous androgen administration (see Schiavi and White, 1976 for review). However, previous investigators have generally failed to distinguish between loss of sexual appetite and erectile disorders. Evidence is mounting that erectile mechanisms per se may be relatively unaffected by androgen status (Bancroft and Wu, 1983) and the relationship between androgens and sexual interest in the male has only recently received serious attention.

Wu et al. (1982) using an experimental rather than a correlational approach, reported the behavioural effects of testosterone administered

to adult Klinefelter men who had exogenous testosterone levels which were in the low to normal range. These authors reported that the principal effect of testosterone administration, as compared with matched placebo treatment, was to increase the frequency of self-rated sexual thoughts and sexual excitement associated with those thoughts. Wu et al. (1982) suggest that further studies are required to determine whether testosterone administration has a similar effect on the sexual behaviour of the endocrinologically normal man. It is important to note that Skakkebaek et al. (1981), in their study of testosterone replacement in hypogonadal men, reported that changes in sex interest were closely related in time to androgen replacement and withdrawal. Similarly Heim and Hursch (1979) in their review of the literature on the effects of castration in the male concluded that while many castrates retained the erectile capacity necessary for intercourse, the majority reported a marked decrease or disappearance of spontaneous interest in sex.

In light of this recent literature suggesting that in the male, sex interest rather than erectile function may be related to androgen status, a controlled investigation into the effects of substantially raising circulating androgen levels in eugonadal men complaining of loss of, or reduced sexual interest appears to be warranted. The rationale behind the present study can be summarised as follows:-

(a) Sexual interest may be that sub-factor of overall male sexual behaviour which is most directly influenced by alterations to circulating androgen levels.

(b) Individuals may differ as to their threshold androgen requirements necessary for a "normal" degree of sexual interest.

(c) Men who complain of reduced interest in sex may benefit from having

their circulating androgen levels raised.

5.2 MATERIALS AND METHODS

5.2.1 Subjects

The sample was recruited from eugonadal male reporters to the local sexual problems clinic (Royal Infirmary of Edinburgh). The recruitment criteria were that the subjects be aged between 18-65 years and whose primary presenting complaint, as determined by the referring therapist and subsequently confirmed by the author, was loss or lack of interest in sex which was not secondary to erectile failure, or any obvious physical or mental illness. Patients were informed of the purpose of the study and were offered the opportunity to participate while on the waiting list for psycho-sexual counselling. Between May 1981 and December 1982, ten subjects aged between 33-64 years (mean 44.6 $\pm$ 10.3 yrs) were recruited. All subjects had a current sexual partner; in fact all were married. Before inclusion in the study each subject was shown to have normal liver function and no indications of prostatic disease, using standard laboratory tests.

5.2.2 Design

For a period of four weeks (which acted as a baseline) subjects had weekly blood samples taken to determine resting endocrinological status. Thereafter subjects were administered Sustanon 250 injections (Organon International Ltd.) intramuscularly every fortnight for six weeks and matched placebo injections fortnightly for six weeks. The design was balanced in that five subjects received the testosterone preparation for the first six weeks, five received the placebo injections first. Sustanon was chosen as the androgen preparation as previous research (described in Chapter 4) had shown that marked elevations in circulating testosterone levels are consistently brought

about by this mode of administration compared with oral androgen preparations.

All injections were administered in a double blind manner.

5.2.2.1 Hormone Measurement

Weekly blood samples (10 mls by venepuncture) were taken at the same time of day (at a time convenient to the subject) throughout the sixteen week study period. Androgen and placebo injections were administered at the same time as the blood sample was taken. Plasma samples were assayed for testosterone using the method of Corker and Davidson (1978) and for SHBG using the method of Anderson et al. (1976).

5.2.2.2 Behavioural Assessment

Each subject completed a coded daily diary form (see Appendix IV) for the duration of the study, indicating presence or absence of morning erections, incidence and description of sexual activity, whether ejaculation resulted and whether the sexual activity was self, partner or jointly initiated. Frequency of sexual thoughts and arousal associated with these thoughts were scored on 100 mm visual analogue scales. Mood state was also evaluated daily by means of ten independent visual analogue scales. The four week baseline phase allowed subjects to become accustomed to completing the diary form on a daily basis prior to entering the study proper. During this period the experimenter checked the forms and advised individuals who were unsure as to what was required.

The experimenter also carried out a structured interview (see Appendix V) at the end of each of the testosterone and placebo treatment periods, rating each subject on various aspects of his sexual functioning, e.g. intercourse frequency, degree of sexual interest,

positive and negative feelings during sexual contact, degree of non-genital arousal during sexual contact, quality of erection, degree of ejaculatory control and receptivity.

5.2.3 Analysis

Mean differences in self-rated (diary) sexual behaviour (testosterone versus placebo treatment) were analysed using the paired t-test. The data from the visual-analogue scales were reduced to weekly means and compared across treatment periods using repeated measures analysis of variance. Interview ratings of sexual functioning were compared across treatments using the Sign Test. The effect of Sustanon injections on circulating testosterone and SHBG levels was assessed using repeated measures analysis of variance.

5.3 RESULTS

The results of the effects of high dosage testosterone injections compared with placebo are summarised in Tables 5.1 to 5.3 and in Figs. 5.1 and 5.2. In Fig. 5.1 the visual analogue scores were standardised using the proportional method (see Chapter 2.1.1). The difference between each subject's weekly mean score and his overall entire study phase mean score was expressed as a percentage of the range of the scale used by that individual. Change scores represent each subject's behavioural rating while receiving testosterone minus his rating while receiving placebo. These values were then meaned for the group as a whole. The observed testosterone effect on frequency of sexual thoughts was not a transient one following the first active injection, as analysis of variance revealed no significant differences in self-rated sexual interest across time ($F=0.23$, N.S.) and there was no evidence of an interaction effect, treatment against time ($F=0.02$, N.S.).

TABLE 5.1 DIARY DATA

THE EFFECT OF HIGH DOSE TESTOSTERONE VERSUS PLACEBO TREATMENT IN MEN COMPLAINING OF REDUCED SEXUAL INTEREST (n=10)

Behavioural measure	Change Score (Testosterone minus Placebo; Mean ± S.D.	Paired t-test
Frequency of Morning Erections (%)	8.4 (16.7)	N.S.
Frequency of Sexual Activity per treatment period	1.2 (3.7)	N.S.
Frequency of Self-Initiated Sexual Activity per treatment period	1.1 (2.4)	N.S.
Visual Analogue Scales (0-100)		ANOVAR
Sexual Thoughts	5.0 (5.3)	$p < 0.02$
Sexual Excitement Associated with Sexual Thoughts	4.4 (7.8)	N.S.
Mood		
Cheerful and Happy	0.6 (5.4)	N.S.
Fatigued and Tired	1.6 (7.2)	N.S.
Sociable and Friendly	1.0 (4.9)	N.S.
Energetic	2.8 (13.5)	N.S.
Tense and Anxious	2 (5.6)	N.S.
Irritable	-2.4 (5.4)	N.S.
Changeable	0.9 (5.2)	N.S.
Aggressive	-0.8 (5.1)	N.S.
Depressed and Unhappy	0.5 (3.6)	N.S.
Relaxed	1.6 (6.5)	N.S.

TABLE 5.2 INTERVIEW DATA

THE EFFECT OF HIGH DOSE TESTOSTERONE VERSUS PLACEBO TREATMENT IN MEN COMPLAINING OF REDUCED SEXUAL INTEREST (n=8)+

Behavioural Measure	No. Improved after Testosterone	No. Deteriorated after Testosterone	Sign Test
Sexual Activity Frequency	4	2	N.S.
Sexual Interest	4	0	$p < 0.1$
Negative Feelings (frequency)	0	0	N.S.
Negative Feelings (strength)	0	0	N.S.
Positive Feelings	0	0	N.S.
Sexual Arousal (frequency)	0	0	N.S.
Sexual Arousal (strength)	2	1	N.S.
Orgasm (frequency)	0	0	N.S.
Erection (quality)	1	2	N.S.
Ejaculation (retarded)	0	0	N.S.
Ejaculation (premature)	0	1	N.S.
Receptivity	2	2	N.S.

+Complete interview data available for 8 out of the 10 subjects

TABLE 5.3 ENDOCRINE DATA (Mean ± S.D)

Hormone nmol/l	Baseline	Sustanon Treatment	Placebo Treatment
Testosterone	23.1(7.0)	31.7**(13.9)	22.9 (7.0)
SHBG	33.5(10.5)	27.6* (8.8)	33.5 (10.5)

ANOVAR ** Sustanon > Baseline, $p < 0.01$
Sustanon > Placebo, $p < 0.01$
* Sustanon < Baseline, $p < 0.05$
Sustanon < Placebo, $p < 0.05$

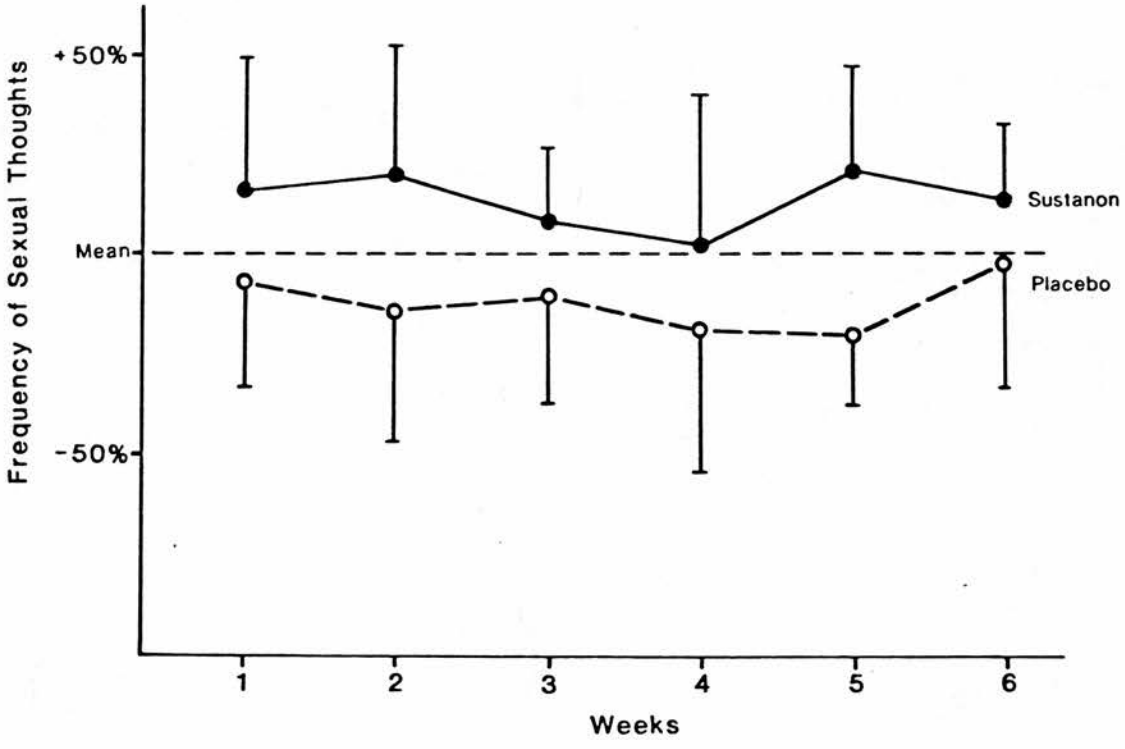

FIGURE 5.1

The effect of Sustanon (testosterone) versus placebo treatment on self-rated frequency of sexual thoughts in ten men complaining of reduced sexual interest. Sustanon > Placebo, $p<0.02$, ANOVAR.

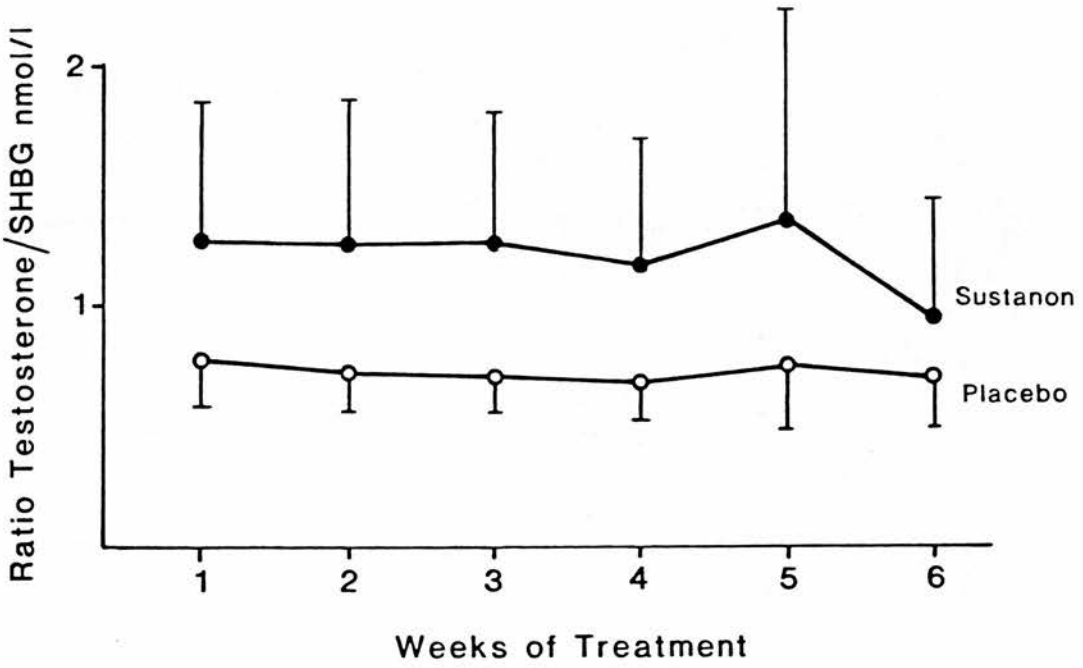

FIGURE 5.2

The effect of Sustanon (testosterone) and placebo treatment on the ratio of $\frac{\text{testosterone}}{\text{SHBG}}$ in 10 men complaining of reduced sexual interest.

There was no correlation between each man's mean basal testosterone level and his percentage increase in sexual interest ($r = -0.18$, N.S.) or between each man's age and percentage increase in sexual interest ($r = 0.33$, N.S.).

5.4 DISCUSSION

The results of the present study indicate that testosterone administration acted to significantly increase circulating total testosterone levels and to decrease circulating SHBG levels, effectively acting to increase the proportion of unbound bio-active androgen in the plasma (Fig. 5.2). This elevation in "free" testosterone level appeared to act to increase the sexual interest of a group of men whose primary complaint was loss of libido (Fig. 5.1). This effect was apparent both when self-ratings and blind assessors interview ratings were analysed.

High dosage testosterone treatment had no effect on mood state. This negative finding is important in light of Kinsey *et al*.s (1953) suggestion that androgens act primarily on general metabolism and mood, and only secondarily on sexual functioning. The present findings are thus in direct opposition to the Kinsey hypothesis.

At present one can only speculate as to the mechanisms underlying the effect of androgen administration on sexual interest. It is possible that certain individuals require a higher theshold level of androgen than others in order to stimulate "normal" sexual appetite. A decrease in the circulating "free" androgen level may act to reduce the level of sex interest in such individuals. Such a decrease in androgen levels could be brought about by environmental factors, e.g. stress (Kreuz *et al*. 1972). The stress produced by marital or sexual problems in a couple could act to make the situation worse. As Carney *et al*.

(1978) state, "prolonged inhibition of sexual response could affect endogenous androgen production, which in turn could serve to exacerbate and prolong the dysfunction". It is perhaps appropriate to state that hormonal factors probably play a minimal role in the development of sexual problems in the majority of eugonadal couples. However, subtle differences in endocrine status may be enough to tip the balance towards dysfunction, e.g. declining sexual interest in the male in a partnership where the man is expected to take the sexual initiative may result in feelings of unattractiveness and rejection in the female, perhaps leading to resentment and hostility. This could then develop into a self-perpetuating "vicious circle" (see Fig. 5.3).

This proposed circle could be broken in a number of ways, e.g. psychotherapeutic counselling for the marital problems, encouraging the female to take the sexual initiative, and perhaps via exogenous androgen administration.

One highly relevant study carried out recently was that of the World Health Organisation task force on psychosocial research in family planning (W.H.O. 1982). The authors investigated the acceptability of hormonal methods of male contraception and their major finding with respect to effects on behaviour was that anti-androgens such as cyproterone acetate acted to decrease the sexual interest and increase the incidence of sexual problems of a group of normal men. However, methyltestosterone administration acted to <u>increase</u> the frequency of sexual thoughts, as assessed by interview ratings, in a group of normal healthy male volunteers. The W.H.O. (1982) authors attached little significance to these stimulatory effects of testosterone administration, and put the results down to small sample size. However, given the W.H.O. (1982) results, combined with the data

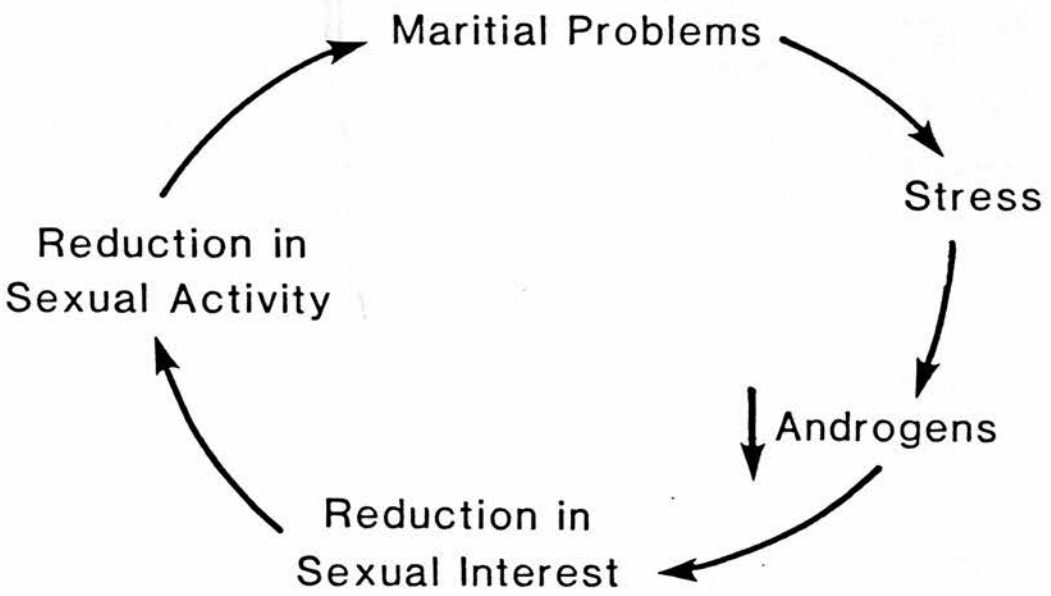

FIGURE 5.3

Hypothesised "vicious circle" implicating androgens and reduced sexual interest in the development and/or maintenance of sexual and marital dysfunction.

supplied by Wu et al. (1982) in their study of testosterone undecanoate administration to Klinefelter men, and the findings of the present study, evidence is mounting suggesting that androgens may have a stimulatory effect on the sexual interest of the eugonadal man.

Longer term replicative studies are required to determine whether this effect of testosterone acting to increase the sexual interest of men complaining of loss of sexual appetite is maintained over longer periods of hormone administration. It is also important to point out that in only three of the ten subjects in the present study did the testosterone induced increase in sex interest act to bring about a significant beneficial effect on the overt sexual behaviour of the couple, i.e. an increase in intercourse frequency. It is possible that the couples' behaviour had become entrained in that sexual activity had become a relatively infrequent occurrence, and given communication difficulties, resentment, hostility, etc. any increase in the sexual appetite of the male brought about by endocrine manipulation, may have been insufficient to overcome the interpersonal conflicts that may have developed. If the findings of the present study are replicated, it is reasonable to suggest that in couples where the major problem appears to be loss of sexual interest in the male, the best mode of therapeutic intervention may be to combine androgen administration with psycho-sexual counselling where the emphasis would be placed upon improving the communication between the couple and where appropriate, encouraging the female to take the sexual initiative.

CHAPTER 6

A CONTROLLED EVALUATION OF TESTOSTERONE TREATMENT IN MEN WITH ERECTILE DYSFUNCTION

6.1 INTRODUCTION

Many investigators studying the relationship between hormones and sexual behaviour in man have tended to use the rather unspecific and general term "impotence" to describe groups of men with various disorders of sexual functioning, e.g. men presenting with loss of sexual interest, premature ejaculation and erectile dysfunction have often been grouped together and studied as a homogeneous patient sample (Schiavi and White, 1976). In this thesis an attempt has been made to introduce operational behavioural definitions of the various male sexual dysfunctions and in the present chapter a study is reported where eugonadal men complaining specifically of erectile dysfunction participated in a controlled trial of the effects of high dosage testosterone treatment.

6.2 MATERIALS AND METHODS

6.2.1 Subjects

The sample was recruited from eugonadal male reporters to the local sexual problems clinic at the Royal Infirmary of Edinburgh. The recruitment criteria were that the subjects be aged 18-65 years and that their primary complaint, as determined by the referring therapist and subsequently by the experimenter, was difficulty in achieving or maintaining a full erection during sexual contact, which was not secondary to loss of sexual interest or any obvious physical or mental illness. Patients were informed of the purpose of the study (i.e. to investigate high dosage testosterone effects on erectile function) and were given the opportunity to participate while on the waiting list for psycho-sexual counselling.

Between May 1981 and December 1982 twelve subjects were recruited. Two subjects dropped out at an early stage, one because he complained of excessive pain following the intra-muscular injections, and the other because of lack of behavioural improvement (it transpired that this particular patient dropped out after receiving three placebo injections). Complete behavioural data was therefore obtained for ten subjects aged between 19-64 years (mean 45.4 $\pm$ 13.0 yrs.). Nine of the ten subjects had current sexual partners (eight were married). Before inclusion in the study each subject was shown to have normal liver function and no indications of prostatic disease, using standard laboratory tests.

6.2.2 Design

The experimental design was exactly the same as that described in Chapter 5, i.e. after a four week baseline period, subjects were administered Sustanon 250 testosterone injections every fortnight for six weeks and matched placebo injections fortnightly for six weeks. The design was balanced in that half the subjects received the active preparation for the first six weeks, half the subjects received the placebo preparation first.

6.2.2.1 Hormone Measurement

As described in Chapter 5, weekly blood samples were taken throughout the sixteen week study period. Plasma samples were assayed for testosterone using the method of Corker and Davidson (1978) and for SHBG using the method of Anderson *et al*. (1976).

6.2.2.2 Behavioural Assessment

The behavioural assessment was as described in Section 5.2.2.

6.2.3 Analysis

The analysis of the results was as described in Section 5.2.3.

6.3 RESULTS

The results of the effects of high dosage testosterone injections compared with placebo are summarised in Tables 6.1-6.3. Change scores represent each subject's behavioural rating while receiving testosterone minus his rating while receiving placebo. These values were then meaned for the group as a whole.

6.4 DISCUSSION

The results again demonstrate that the testosterone injections acted to significantly increase circulating total testosterone levels and to decrease circulating SHBG levels, effectively acting to increase the proportion of unbound bio-active androgen in the plasma. This elevation in the "free" testosterone level was entirely without behavioural effect on any of the measures of sexual functioning or mood state.

This is the first controlled study to be carried out investigating the efficacy of androgen administration in the treatment of erectile dysfunction where evidence has been presented demonstrating that the androgen administration resulted in a significant elevation in circulating testosterone levels ($p < 0.01$). Previous investigators have either not measured blood androgen levels following treatment (e.g. Jakobovitz, 1970) or where endocrine measures have been carried out, androgen administration failed to overcome the eugonadal homeostatic

TABLE 6.1 DIARY DATA

THE EFFECT OF HIGH DOSE TESTOSTERONE VERSUS PLACEBO TREATMENT IN MEN COMPLAINING OF ERECTILE DYSFUNCTION (n=10)

Behavioural measure	Change Score (Testosterone minus Placebo; Mean ± S.D.	Paired t-test
Frequency of Morning Erections (%)	2.4 (8.5)	N.S.
Frequency of Sexual Activity per treatment period	0.44 (0.5)	N.S.
Frequency of Self-Initiated Sexual Activity per treatment period	0.5 (2.6)	N.S.
Visual Analogue Scales (0-100)		ANOVAR
Sexual Thoughts	2 (6.5)	N.S.
Sexual Excitement Associated with Sexual Thoughts	2 (4.1)	N.S.
Mood		
Cheerful and Happy	3.2 (6.8)	N.S.
Fatigued and Tired	5.1 (8.7)	N.S.
Sociable and Friendly	2.6 (6.4)	N.S.
Energetic	3.4 (6.6)	N.S.
Tense and Anxious	3 (9.9)	N.S.
Irritable	4.6 (9.1)	N.S.
Changeable	2.3 (11)	N.S.
Aggressive	4.1 (10.8)	N.S.
Depressed and Unhappy	-3.3 (12.2)	N.S.
Relaxed	1 (10.5)	N.S.

TABLE 6.2 INTERVIEW DATA

THE EFFECT OF HIGH DOSE TESTOSTERONE VERSUS PLACEBO TREATMENT IN MEN COMPLAINING OF ERECTILE DYSFUNCTION (n=9)+

Behavioural Measure	No. improved after Testosterone	No. Deteriorated after Testosterone	Sign Test
Sexual Activity Frequency	5	3	N.S.
Sexual Interest	2	2	N.S.
Negative Feelings (frequency)	0	2	N.S.
Negative Feelings (strength)	1	0	N.S.
Positive Feelings	0	0	N.S.
Sexual Arousal (frequency)	0	2	N.S.
Sexual Arousal (strength)	0	1	N.S.
Orgasm (frequncy)	3	2	N.S.
Erection (quality)	3	1	N.S.
Ejaculation (retarded)	0	0	N.S.
Ejaculation (premature)	0	2	N.S.
Receptivity	0	0	N.S.

+Complete interview data available for 9 out of the 10 subjects.

TABLE 6.3 ENDOCRINE DATA (Mean ± S.D.)

Hormone nmol/l	Baseline	Sustanon Treatment	Placebo Treatment
Testosterone	16.8(5.4)	20.5** (7.3)	14.3 (5.9)
SHBG	30.4(10.7)	24.3* (8.5)	27.7 (9.6)

ANOVAR ** Sustanon > Placebo, $p < 0.01$
Sustanon > Baseline, $p < 0.05$
* Sustanon < Placebo, $p < 0.05$
Sustanon < Baseline, $p < 0.05$

mechanisms and treatment did not result in an elevation of circulating androgen levels (e.g. Benkert et al. 1979).

General clinical opinion over the past fifteen years has subscribed to the view that androgen treatment is unhelpful in the treatment of erectile dysfunction unless the individual suffers from a genuine deficiency, e.g. "Androgens...are useless as a treatment of impotence unless it accompanies hypogonadism" (British Medical Association, 1981). The present chapter reports the first study which has actually tested and confirmed this hypothesis.

However, given the stimulatory effect of testosterone injections on sexual interest in the treatment of eugonadal men complaining of loss of libido (described in Chapter 5), it is perhaps surprising that in the present study, androgen administration had no effect on sexual interest in men complaining of erectile dysfunction (particularly as the men with erectile problems had slightly lower mean endogenous testosterone levels than the men with reduced sexual interest, 16.8 (5.4) and 23.1 (7.0) nmol/l respectively). There are two possible explanations for these different behavioural effects of testosterone administration in the two patient groups:-

(a) The men with erectile dysfunction had a relatively "normal" degree of sexual interest. (At initial interview, these men reported thinking about sex with appetite and desire, on average several times per week as opposed to the low libido men who on average reported thinking about sex more than once per month but less than once per week). Therefore the men with erectile dysfunction had less scope for androgen stimulated improvement in sex interest compared with the low libido group.

(b) Men may have a threshold level of circulating testosterone for optimal sexual appetite and any experimentally induced elevation in circulating testosterone levels above this threshold would have no behavioural effect (Raboch and Starka, 1972; Pirke and Kockott, 1982). However, this threshold level may not be an absolute one across subjects (i.e. x nmol/l); individuals may vary as to their optimal level of circulating testosterone. It is possible that the men complaining of loss of sexual interest (described in Chapter 5) were, on average, below their optimal level whereas the men complaining of erectile dysfunction (described in the present chapter) were, on average, above their optimal threshold level of circulating testosterone, and were thus unaffected by exogenous androgen administration. This hypothesis would account for the observation that some hypogonadal men retain a relatively normal degree of sexual interest and activity, despite having very low circulating levels of testosterone (e.g. as described by Salmimies et al. 1982). Presumably in these hypogonadal men the optimal threshold level of circulating androgens is markedly lowered in comparison with other men, i.e. they have a heightened sensitivity to the behavioural effects of testosterone.

The present author would propose that if androgens act primarily on sexual appetite, as suggested by Bancroft (1980), then androgen treatment may be helpful in certain cases where the individual complains of loss of sexual interest with relatively undisturbed erectile function. However, androgen administration probably has no more than a placebo effect in the treatment of erectile disorders in the eugonadal man.

CHAPTER 7

THE EFFECT OF ANDROGEN ADMINISTRATION ON NOCTURNAL ERECTIONS IN HYPOGONADAL AND EUGONADAL MEN

7.1 INTRODUCTION

As reviewed in Chapter 1.5, several claims have been made in the literature suggesting that a relationship exists between androgen status and nocturnal erectile function in men. In particular Kwan et al. (1983) demonstrated that in the hypogonadal man, episodes of nocturnal penile tumescence (NPT) are reduced following androgen withdrawal, and Jovanovic and Tan-eli (1969) reported that eugonadal men complaining of erectile impotence displayed NPTs which were markedly impaired when compared with age-matched controls, and that treatment with a methyl-testosterone preparation acted to improve and "normalise" their nocturnal erections.

As the results of both of these studies are unsubstantiated, and as both investigations are open to criticism (i.e. Jovanovic and Tan-eli (1969) failed to provide clinical details of their patient group and Kwan et al. (1983) used portable home monitors for self-assessment of nocturnal erectile function), an attempt is made in this chapter to replicate their findings.

7.2 MATERIALS AND METHODS

7.2.1 Subjects

7.2.1.1 Hypogonadal Subjects

All of the hypogonadal subjects described in Chapter 3 were invited to participate in sleep recordings where nocturnal erectile function would be directly measured "on" and "off" androgen replacement. This involved:-

(a) Two consecutive nights of assessment to be carried out a minimum of eight weeks after cessation of their previous androgen replacement

(b) Two consecutive nights of assessment to be carried out a minimum of five months after re-starting replacement with testosterone undecanoate (i.e. four months of varying the replacement dose of T.U. (as described in Chapter 3) plus a minimum of one month on the dosage of T.U. which had produced the best behavioural results in that individual - on average 120-160 mg T.U./day).

Only three out of the eight hypogonadal men described in Table 3.1 (nos. 1,4 and 8) agreed to participate. An additional 40 year old hypogonadotrophic hypogonadal man was therefore recruited and underwent NPT assessment while markedly hypogonadal (mean testosterone level = 3.2 nmol/l; he had received no androgen replacement for the previous seven years). He was then re-assessed for NPTs after two months of highly efficacious treatment with T.U. 160 mg/day.

Thus a total of four hypogonadal men were assessed for nocturnal erectile function for two consecutive nights while in a markedly hypogonadal state and were then re-assessed for two consecutive nights after receiving testosterone replacement.

In order to investigate the effect of longterm androgen withdrawal on nocturnal erectile function, a 35 year old hypogonadotrophic hypogonadal man who had elected to stop taking his androgen replacement underwent NPT assessment on two occasions. The subject was monitored in the sleep laboratory for two consecutive nights after eight weeks withdrawal from androgens. This was repeated after one year's withdrawal.

7.2.1.2 Eugonadal Subjects

All the eugonadal subjects complaining of erectile dysfunction (described in Chapter 6) were similarly asked whether they would be

prepared to participate in research into the effects of androgens on nocturnal erectile function. Subjects were informed that this would entail spending a total of four nights in the sleep laboratory, two successive nights during the week following their third injection and two successive nights during the week following their sixth injection (i.e. NPT assessments were carried out in the week following the last testosterone injection and in the week following the last placebo injection - see Chapter 6). Nocturnal erections were thus measured after six weeks of high dosage testosterone treatment and again after six weeks of matched placebo treatment.

Seven eugonadal men agreed to participate (mean age 48.4 $\pm$ 16.4 years), with a duration of erectile dysfunction which ranged from 3-10 years (mean 4.8 years). Four subjects received the testosterone injections as their first treatment followed by placebo injections, three subjects were given the placebo injections first.

7.2.2 Design

Subjects were taken into the sound dampened and temperature controlled sleep laboratory in the Royal Edinburgh Hospital at 2200 hours on the first NPT assessment night, and the experimental procedure was explained. A mercury-in-rubber strain gauge with platinum electrodes (Bancroft, 1974) was fitted, by the subject, around the base of his penis, the lead from the strain gauge being firmly attached to the patient's abdomen with elastoplast. The strain gauge was calibrated using two perspex disc standards of differing diameters (25 and 26 mm). Calibration was carried out before and after each night of NPT recording so that any changes in penile diameter could be readily and accurately measured. The electrode leads were fed into a Grass model 7D polygraph recorder situated in a room adjacent to the sleep laboratory. Subjects were settled in bed at approximately 2230 hrs.,

with lights off at 2300 hrs. Subjects were awakened at 0700 hrs on the following morning.

Each subject was assessed for two consecutive nights "on" and two consecutive nights "off" androgens. The first night of each assessment session was used as an adaptation night to accustom the subject to the sleep laboratory and the recording procedure. (First night measures are not reported in this chapter). All NPT assessments and subsequent analysis were carried out by the author. In total forty-eight nights of NPT recordings were performed.

7.2.3 Analysis

Any definition of erection based upon penile diameter change from basal (i.e. flaccid) is somewhat arbitrary given the large degree of variation that exists between subjects (Schiavi and Fisher, 1982). For this reason, two definitions of erection, taken from the research literature, were used in the analysis. Marshall et al. (1981) defined an NPT episode as a 3 mm increase in penile circumference from basal (i.e. flaccid). Hosking et al. (1979) and Kwan et al. (1983) however used a more selective criterion of erection, i.e. greater than or equal to 15 mm circumference increase from basal.

In the present study, by analysing the data twice, using these two very different decision rules as to what constitutes an NPT episode, any hormone mediated effects on nocturnal erectile function should become apparent.

Frequency, duration, latency to first erection, latency to maximum erection, maximum erection attained and total tumescence time were compared, testosterone treatment versus no treatment (in the hypogonadal men) and testosterone versus placebo treatment (in the eugonadal men).

The paired t-test (one-tailed) was used to compare differences across treatments.

7.3 RESULTS

The results of the effects of androgen administration on NPTs in the hypogonadal men are shown in Table 7.1 and in the eugonadal men in Table 7.2. The change scores represent each subject's NPT value while receiving testosterone minus his NPT while receiving no treatment (hypogonadal) or placebo (eugonadal). These differences were then meaned for the group as a whole.

The NPTs of a hypogonadal man recorded after eight weeks and again after one year of withdrawal from androgens are shown in Figure 7.1

7.3.1 Order Effect?

The results demonstrate that the NPTs of eugonadal men complaining of erectile dysfunction were unaffected by androgen administration whereas the nocturnal erections of hypogonadal men were markedly affected by androgen administration. However, it is possible that the different results obtained in the two patient groups are the result of an order rather than a genuine hormone mediated effect. The design of the hypogonadal study was not controlled for order in that all the hypogonadal subjects underwent initial NPT assessment while markedly hypogonadal and this was followed by re-assessment of nocturnal erectile function after several months of androgen replacement therapy. An attempt was made to control for an order effect in the eugonadal group in that four subjects received the testosterone injections as their first course of treatment, three received placebo first. To investigate the possibility of an order effect in the eugonadal group, the NPT parameters were compared first assessment session versus second

TABLE 7.1

THE EFFECT OF T.U. TREATMENT ON NOCTURNAL ERECTILE FUNCTION IN FOUR HYPOGONADAL MEN

NPT Measure	Change Score (Testosterone minus Basal; Mean ± S.D.)	Paired t-value	Significance level
Max. Circumference Change (m.m.)	32.8 (26.3)	2.49	$p < 0.05$
Latency to Max. Erection (mins.)	74.0 (216.1)	0.51	N.S.
Erection $\geq$ 15 mm NPT Frequency	1.0 (2.8)	0.71	N.S.
Total NPT Duration (mins.)	38.9 (31.6)	2.46	$p < 0.05$
Latency to First Erection (mins.)	-218.1 (161.7)	2.69	$p < 0.05$
Erection $\geq$ 3 mm NPT Frequency	1.25 (3.5)	0.71	N.S.
Total NPT Duration (mins.)	73.7 (36.2)	4.07	$p < 0.025$
Latency to First Erection (mins.)	-70.7 (123.8)	1.10	N.S.

TABLE 7.2

THE EFFECT OF TESTOSTERONE TREATMENT ON NOCTURNAL ERECTILE FUNCTION IN SEVEN EUGONADAL MEN

NPT Measure	Change Score (Testosterone minus Basal; Mean ± S.D.)	Paired t-value	Significance level
Max. Circumference Change (m.m.)	-2.45 (13.1)	0.48	N.S.
Latency to Max. Erection (mins.)	-7.34 (121.7)	1.07	N.S.
Erection ≥ 15 mm NPT Frequency	0.28 (1.2)	0.882	N.S.
Total NPT Duration (mins.)	5.4 (33.8)	0.143	N.S.
Latency to First Erection (mins.)	-38.9 (80.6)	0.239	N.S.
Erection ≥ 3 mm NPT Frequency	0.0 (2.4)	0.00	N.S.
Total NPT Duration (mins.)	1.03 (102.3)	0.33	N.S.
Latency to First Erection (mins.)	0.24 (64.1)	0.34	N.S.

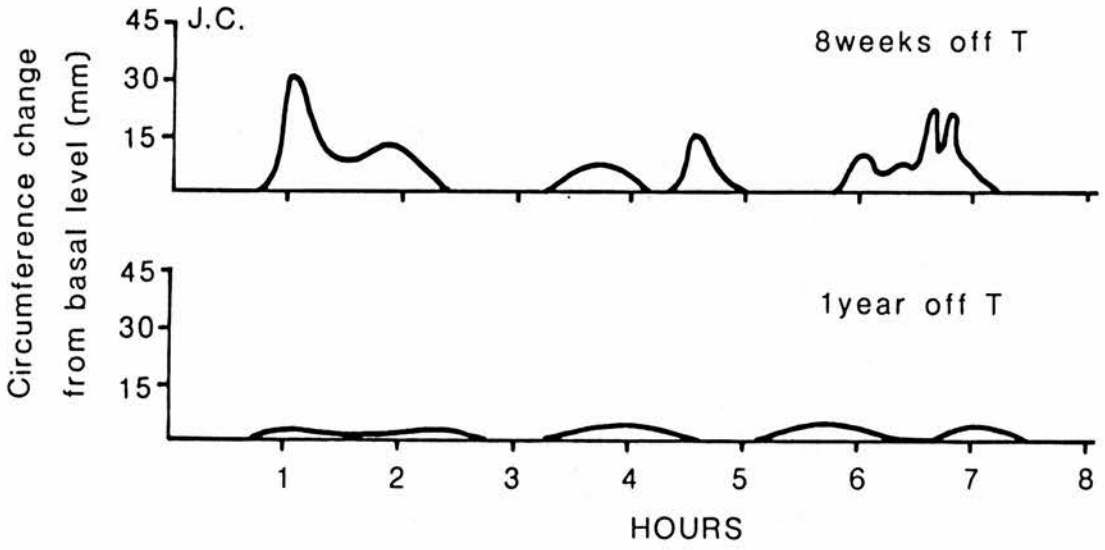

FIGURE 7.1

Nocturnal erectile function in a hypogonadal man, eight weeks and one year after withdrawal from androgen replacement.

assessment for each subject. All comparisons were non-significant using the paired t-test.

This result suggests that the significant improvement in nocturnal erectile functioning observed in the hypogonadal patients was a genuine result of the androgen treatment and was not the result of an order effect.

7.4 DISCUSSION

7.4.1 Hypogonadal Subjects

Androgen treatment had a marked effect on the NPTs of the hypogonadal subjects (Table 7.1). T.U. replacement acted to increase the magnitude of the maximum nocturnal erections attained and also acted to increase the total time spent in penile tumescence. This effect was apparent using both the 3 mm and 15 mm definitions of erection. These results are almost identical to those reported by Kwan et al. (1983).

Interestingly, nocturnal erection frequency (i.e. number of erections per night) was not significantly increased in the hypogonadal group following androgen replacement. This was possibly due to the fact that one of the subjects (No.8) displayed a marked degree of nocturnal erectile function while "off" androgens for eight weeks. This atypical retention of nocturnal erectile response is similar to the pattern of NPTs exhibited by the hypogonadal subject whose nocturnal erections were recorded after eight weeks and again after one year of androgen withdrawal (Figure 7.1). This man also retained a marked degree of nocturnal erectile function eight weeks after androgen withdrawal but one year after cessation of treatment, no nocturnal erections were observed.

The results of this study suggest that there may be a variable rate of decline of androgen dependent nocturnal erectile function, most hypogonadal men demonstrating a marked diminution in erectile response eight weeks after androgen withdrawal, with other hypogonadal men retaining a degree of nocturnal erectile activity for longer periods of time.

7.4.2 Eugonadal Subjects

As illustrated in Table 7.2, androgen treatment had no effect on any of the measures of nocturnal erectile function in the eugonadal group. Using both Hosking et al.'s (1979) $\geqslant$ 15 mm and Marshall et al's (1981) $\geqslant$ 3 mm circumference change from basal definitions of erection, frequency, duration, latency to first erection, latency to maximum erection, maximum erection attained and total tumescence time were all unaffected by high dosage testosterone administration compared with matched placebo. These results are contrary to those published by Jovanovic and Tan-eli (1969). However, three important differences exist between the two studies which may account for these discrepant findings:-

(a) The endocrine status and the clinical details of the patients in the study of Jovanovic and Tan-eli (1969) were not reported - it is possible that their patients' erectile disorders could have been secondary to hypogonadism, which could account for the beneficial effects of testosterone treatment.

(b) Their study was not blind and no placebo was used, therefore a degree of bias may have been introduced.

(c) The methyl-testosterone preparation that these authors used also contained a number of psycho-active agents, e.g. caffeine and

strychnine, although the authors reported that "testosterone is essential because of its androgenic, roborant, anabolic and stimulatory effect" (Jovanovic and Tan-eli, 1969). Cooper et al. (1973) using a similar preparation found slight and transient improvements in the treatment of erectile impotence but concluded that these beneficial effects were due to the central nervous system stimulation caused by the non-steroid constituents of the preparation.

In conclusion, in the hypogonadal man withdrawal from androgen treatment was shown to act to reduce NPT activity, although diminution of erectile response occurred at a variable rate. Androgen replacement to hypogonadal men acted to stimulate nocturnal erectile function, in particular total duration of tumescence and maximum erection attained were significantly increased following testosterone replacement therapy. In the eugonadal man complaining of erectile dysfunction, androgen administration had no effect on nocturnal erectile function.

These results are consistent with the hypothesis that a certain threshold level of circulating androgen is required for normal male sexual functioning (Chapter 6). Presumably the untreated hypogonadal subjects were below their optimal testosterone level and androgen treatment acted to stimulate their nocturnal erections. The eugondal men however were presumably above their theshold testosterone level and exogenous androgen administration had no effect.

The present results, and those supplied by Kwan et al. (1983) tend to suggest that nocturnal erections are reduced by androgen withdrawal and stimulated following androgen replacement. This observation has to be discussed in light of Bancroft's (1980) hypothesis that erectile function is independent of androgen status in man. Nocturnal erections

are presumably responses to some central event and it may be that it is this central process rather than the erectile mechanisms *per se* which is dependent on an adequate level of circulating androgens.

7.4.3 Methodological Point Concerning Arbitrary Definitions of Erection

One point which emerged during the analysis of the NPT records in the present study was the dubious validity of the Marshall *et al.* (1981) definition of an erectile episode. These authors proposed that an erection occurred when there was an increase in penile circumference greater than or equal to 3 mm from basal, that is less than a 1 mm increase in penile diameter. Given the presence of movement artefacts, changes in baseline levels throughout the night, etc., the present author found it quite difficult to judge when such small variations in penile size constituted a true NPT episode. Using the stricter criterion (greater than or equal to 15 mm circumference change from basal) suggested by Hosking *et al* (1979) and Kwan *et al.* (1983), no such difficulties were encountered.

CHAPTER 8

ANDROGEN ADMINISTRATION TO HYPOGONADAL AND EUGONADAL MEN - EFFECTS ON MEASURES OF PERSONALITY AND SPATIAL ABILITY

8.1 INTRODUCTION

As reviewed in Chapter 1.7, several investigators have proposed that androgen levels are correlated with certain measures of non-sexual behaviour in the adult human male. Focusing particularly on spatial ability and the personality measures of Eysenck and Zuckerman, an attempt was made to investigate whether these measures are sensitive to changes in the endocrinological status of the hypogonadal and the eugonadal man.

8.2 MATERIALS AND METHODS

8.2.1 Hypogonadal Subjects

All of the hypogonadal men (N=8) who participated in the investigations described in Chapter 3 agreed to complete a psychometric test battery (see below) on two separate occasions. Each man was withdrawn from his previous androgen replacement for a minimum of eight weeks and was then administered the psychometric test battery. For four successive months each subject was treated with 40, 80, 120 and 160 mg oral testosterone undecanoate (T.U.) per day. Each subject was then placed on long-term replacement with the dose of T.U. which had produced the best behavioural results for that individual (on average 120-160 mg/day). After a minimum of one month on this final dose (i.e. after a total of at least five months treatment with T.U.) the hypogonadal subjects were re-tested.

8.2.2 Eugonadal Subjects

Sixteen of the eugonadal subjects who participated in the investigations described in Chapters 5 and 6 also agreed to complete the psychometric test battery on two separate occasions. Nine of the men were recruited from the erectile dysfunction group and seven men

came from the reduced sexual interest group. The eugonadal subjects received Sustanon 250 injections every two weeks for six weeks and matched placebo injections every two weeks for six weeks. The study was balanced in that eight men received the testosterone injections as their first course of treatment, eight received placebo first. Subjects completed the psychometric test battery twice, (a) after six weeks of high dose testosterone treatment and (b) after six weeks treatment with matched placebo.

8.2.3 The Psychometric Test Battery

8.2.3.1 Assessment of Spatial Ability

Factor analytic studies have demonstrated that the term "spatial ability" is a misnomer and that spatial ability as such is subdividided into two factors, spatial visualisation and spatial orientation (McGee, 1979). Visualisation ability refers to the ability to mentally manipulate and rotate subjects in space, whereas orientation describes the ability to accurately identify objects and their position in relation to the environment. The Revised Minnesota Paper Form Board Test (MPFBT), Form AA (Likert and Quasha, 1970) was used to measure spatial visualisation, and a modified version of the Embedded Figures Test or EFT (Morrison, 1976) was used to assess spatial orientation ability. This version of the EFT consists of twelve items selected from Witkin's test for individual administration (Witkin et al. 1971). These were practice figure P-X, nos. 5,6,8,10,11,13,15,18,19,22 and 23. The figures were reproduced in the test answer book, each with five alternative simple figures of which only one was embedded in the corresponding complex figure. Subjects were instructed to pick out the simple shape contained in the complex design and to record their answer

in the answer column. A time limit of ten minutes was assigned to the task. A copy of the test appears as Appendix VI. This shortened version of the EFT was used in preference to the standard EFT for individual administration (Witkin et al. 1971) because of the need for a brief (ten as opposed to thirty-six minutes required for assessment) and easily administered measure of spatial orientation, in view of the demands being made on the subjects (i.e. the other tests in the psychometric battery). One major difference between the version of the EFT used in this study and Witkin's standard EFT is that in Morrison's modified test, the subject is allowed to inspect the simple shape and complex design simultaneously. In the opinion of the present writer, this approach facilitates direct assessment of the ability to disembed figures, whereas Witkin's original method (where subjects are prevented from viewing the simple shape and complex design simultaneously) introduces a short-term memory factor.

8.2.3.2 Assessment of Personality

The most recent form of Eysenck's personality measures, the Eysenck Personality Questionnaire or EPQ (Eysenck and Eysenck, 1975) was used to assess the effect of androgen administration on extraversion (E), neuroticism (N), psychoticism (P) and Lie (L) scores. Similarly, the Sensation Seeking Scale (SSS) Form IV, as described by Zuckerman (1979) was employed to evaluate the effects of androgen administration on the five SSS subscales, namely General Sensation Seeking (Gen), Thrill and Adventure Seeking (TAS), Experience Seeking (ES), Disinhibition (Dis) and Boredom Susceptibility (BS).

As we are effectively altering the male sex hormone balance of the hypogonadal and eugonadal men, it was also decided to include a measure

of self-rated psychological masculinity and femininity in the psychometric test battery, namely the Bem Sex Role Inventory or BSRI (Bem, 1974). This scale is based upon Bem's philosophical standpoint that behavioural masculinity and femininity are not extremes of a single dimension but are in fact orthogonal. Evidence has been presented suggesting that the BSRI is a reliable and valid form of assessment (Wakefield et al. 1976; Carlsson & Magnusson, 1980). The BSRI classifies individuals on three scales, masculinity (M), femininity (F) and androgyny (And), and has the advantage of being brief and easily administered.

To reiterate, a group of hypogonadal and a group of eugonadal subjects completed a psychometric test battery on two occasions, "on" and "off" androgen treatment. The test battery comprised the Eysenck Personality Questionnaire, the Bem Sex Role Inventory, the Sensation Seeking Scale, the Revised Minnesota Paper Form Board Test and the Embedded Figures Test.

8.2.4 Analysis

Psychometric test scores were analysed for intra-individual change as a result of androgen treatment using the paired t-test.

8.3 RESULTS

The results for the hypogonadal subjects are summarised in Table 8.1 and the results for the eugonadal subjects are summarised in Table 8.2. Change scores were calculated by subtracting the test scores obtained for each individual during the baseline (hypogonadal) or placebo (eugonadal) period from his test score while receiving testosterone. These differences were then meaned for the group as a whole.

TABLE 8.1

PSYCHOMETRIC TEST BATTERY SCORES FOR EIGHT HYPOGONADAL MEN, AFTER 8 WEEKS WITHDRAWAL FROM ANDROGEN REPLACEMENT AND AFTER A MINIMUM OF 5 MONTHS OF TREATMENT WITH TESTOSTERONE UNDECANOATE

Psychometric Measure*	Change Score (Testosterone minus Baseline) Mean ± S.D.	Paired t-test
Bem Sex Role Inventory		
Mas.	0.063 (0.28)	N.S.
Fem.	0.198 (0.34)	N.S.
And.	0.312 (0.99)	N.S.
Sensation Seeking Scale		
Gen.	0 (1.3)	N.S.
T.A.	-0.63 (1.5)	N.S.
E.S.	-0.5 (0.9)	N.S.
Dis.	0 (1.85)	N.S.
B.S.	-0.75 (1.66)	N.S.
E.P.Q.		
P.	-0.38 (0.74)	N.S.
L.	-0.125 (2.53)	N.S.
E.	-0.25 (1.83)	N.S.
N.	0.75 (2.1)	N.S.
Spatial Tests		
EFT	0 (1.7)	N.S.
MPFBT	0.57 (8.9)	N.S.

*See text for details

TABLE 8.2

PSYCHOMETRIC TEST BATTERY SCORES FOR SIXTEEN EUGONADAL MEN, AFTER 6 WEEKS OF HIGH DOSAGE TESTOSTERONE INJECTIONS AND AFTER 6 WEEKS OF MATCHED PLACEBO INJECTIONS

Psychometric Measure*	Change Score (Testosterone minus Placebo) Mean ±S.D.	Paired t-test
Bem Sex Role Inventory		
Mas.	0.17 (0.37)	N.S.
Fem.	0.19 (0.40)	N.S.
And.	0.14 (0.94)	N.S.
Sensation Seeking Scale		
Gen.	0.46 (1.9)	N.S.
T.A.	-0.07 (1.8)	N.S.
E.S.	0.73 (1.9)	N.S.
Dis.	-0.2 (1.3)	N.S.
B.S.	0.53 (1.8)	N.S.
EPQ		
P.	0 (1.03)	N.S.
L.	0.06 (3.9)	N.S.
E.	-0.06 (1.3)	N.S.
N.	1.0 (1.78)	$p<0.01$
Spatial Tests		
EFT	0.3 (1.7)	N.S.
MPFBT	-1.18 (6.7)	N.S.

*See text for details

8.4 DISCUSSION

8.4.1 Tests of Spatial Ability

The results, as displayed in Tables 8.1 and 8.2 demonstrate that androgen administration had no effect on the spatial performance of hypogonadal or eugonadal men. The eugonadal results tend to oppose the hypothesis that a relationship exists between androgenicity and spatial ability in the normal adult male, as has been previously suggested (Broverman et al. 1968; Klaiber et al. 1967; Petersen, 1976), as experimentally induced elevations in plasma androgen levels had no effect on spatial test scores.

The observation that the spatial ability of the hypogonadal man was not improved following testosterone treatment confirms the findings of Hier and Crowley (1982) who reported that three months of androgen replacement did not result in improved spatial performance in a group of hypogonadal men. Taken together, the data supplied by Hier & Crowley (1982) and the results of the present study provide serious opposition to the hypothesis put forward by Bancroft (1980) who, in attempting to account for the observation that the ability of hypogonadal men to produce erections in response to erotic fantasy waxed and waned with androgen replacement and withdrawal (Bancroft & Wu, 1983), proposed that androgens may act to facilitate the visuo-spatial cognitive process in a non-specific manner. The Bancroft (1980) hypothesis is made to look even more suspect in light of the recent failure to replicate the Bancroft & Wu (1983) study. Kwan et al. (1983) reported that the ability to produce erections in response to erotic fantasy was relatively unaffected by androgen replacement and withdrawal. (It is important to point out that

although Kwan et al. (1983) concluded that the erectile responses of the hypogonadal group as a whole to erotic film and fantasy were not significantly affected by androgen administration, three out of the six hypogonadal men produced erections in response to fantasy which were below or at the bottom of the range for normal men, and androgen treatment resulted in an increased erectile response to erotic fantasy in two out of these three subjects). Kwan et al. (1983) suggest that the conflicting results obtained in their study as compared with the Bancroft & Wu (1983) study may be accounted for by cultural differences between California and Scotland, or by chance sampling of different patient types. In the opinion of the present author the latter explanation would appear to be more feasible given the small number of subjects used in each study, six and eight respectively. An alternative explanation for the conflicting results obtained in these two studies is that weaker erotic stimuli may be affected most easily by androgen withdrawal, and films may be more powerful than fantasy in this respect (Bancroft, 1980). It is possible that the hypogonadal men in the Kwan et al. (1983) study may simply have been better at producing more stimulating erotic fantasies than the men in the Bancroft & Wu (1983) study.

As only one out of the eight hypogonadal patients in the present study suffered from idiopathic hypogonadotrophic hypogonadism (IHH), the hypothesis put forward by Hier and Crowley (1982) that IHH men have markedly impaired spatial ability when compared with men with acquired hypergonadotrophic hypogonadism could not be tested. Taking the hypogonadal groups as a whole, comparing their spatial performance with the eugonadal group while on no treatment, no significant differences between the groups were observed for either test of spatial ability.

In conclusion the results of the present study fail to support the hypothesis proposed by Bancroft (1980), i.e. that androgen replacement acts to facilitate visuo-spatial ability in the hypogonadal man. However, the eugonadal results do not enable us to reject the general hypothesis that androgens are involved in the regulation of spatial ability in the human male. In the present study, short-term androgen administration had no effect on spatial test scores but it is possible that androgens have important organisational effects on the central nervous system at critical periods in development and thus influence later visuo-spatial performance.

8.4.2 Personality Measures

8.4.2.1 The Sensation Seeking Scale

In two separate studies, Daitzman *et al.* (1978) and Daitzman & Zuckerman (1980), the authors claimed that significant correlations existed between circulating androgen levels and sensation seeking behaviour, particularly between testosterone levels and the Disinhibition (Dis) subscale of Zuckerman's inventory. To the author's knowledge, the present study was the first experiment to be carried out where androgen levels were manipulated in hypogonadal and eugonadal men and changes in Sensation Seeking Scale scores monitored. Tables 8.1 and 8.2 demonstrate that androgen administration had no effect on any of the SSS scores in either of the subject groups. From the results of this experiment no support can be drawn for the hypothesis proposed by Daitzman *et al.* (1978), Daitzman & Zuckerman (1980) and Zuckerman *et al*(1980), i.e. that a relationship exists between gonadal hormone levels and SSS scores. In both hypogonadal and eugonadal groups of men, androgen levels were experimentally elevated with no consequent effect on SSS scores. However, one must bear in mind the questionable

sensitivity of these psychometric measures to short-term alterations in the endocrine status of the groups being studied.

8.4.2.2 The Eysenck Personality Questionnaire

H.J. Eysenck has repeatedly proposed that the biological basis of his new P scale is closely related to the level of the male sex hormones (see Chapter 1.7.1 for review). The findings of the present study fail to support this hypothesis. Testosterone administration to hypogonadal men had no effect on the P, L, E or N scores of Eysenck's EPQ, and similarly a course of high dosage testosterone injections had no effect on the P, L or E scores of a group of eugonadal men. However, the N scores of the eugonadal men were significantly elevated following androgen treatment as compared with placebo treatment. This is a surprising finding because:-

(a) Eysenck has implicated androgen levels only with his P scale

(b) Androgen administration had no effect on N scores in the hypogonadal group

(c) Kaiser et al. (1978) reported that five weeks of treatment with mesterolone 75 mg/day acted to decrease neuroticism and increase extraversion scores in a group of elderly men

(d) Androgen administration had no effect on "neurotic" mood ratings in the eugonadal group, as assessed by the visual analogue scales in the studies described in Chapters 5 and 6. In these studies subjects rated themselves on a daily basis on scales labelled Tense and Anxious, Irritable, Changeable and Up and Down, etc. and high dosage testosterone injections had no effect compared with placebo on any of these measures of mood. The present writer would tentatively suggest

that these daily assessments (N=42 per treatment period) would have been more sensitive and more likely to "pick up" any genuine androgen induced effect on neurotic behaviour. (However, it could be argued that daily ratings of mood may not be the best method of measuring an androgen induced shift in tonic mood state, and that daily scales are more suitable for picking up day-to-day fluctuations).

Inspection of the actual item content of the N scale of the EPQ does not shed any light on these contradictory findings as most of the questions deal with general worry and nervousness. It is possible that the significant elevation in N scores following androgen administration is due to chance alone. However, the author is aware that the level of significance ($p < 0.01$) makes this a somewhat unsatisfactory explanation.

The correlation between Eysenck's personality dimension and androgen level was originally investigated by Daitzman (1976). It is fascinating to note that although Eysenck proposes a relationship between androgens and psychoticism, Daitzman (1976) in fact reported stronger positive correlations between circulating androgen levels and neuroticism than with psychoticism. Obviously further research is necessary before firm conclusions can be made concerning the relationship (if any) between Eysenck's personality measures and gonadal hormone status, but the evidence to date would tend to support a stronger case for a relationship existing between androgens and N than for androgens and P.

8.4.2.3 The Bem Sex Role Inventory

Androgen treatment had no effect on self-rated masculinity, femininity or androgyny in the groups of hypogonadal and eugonadal men.

Daitzman and Zuckerman (1980) claimed that circulating testosterone levels were negatively correlated with self-rated MMPI femininity in a group of forty young male American students. One would then perhaps have predicted that hypogonadal men would rate themselves as relatively feminine on account of their very low circulating testosterone levels, and for androgen treatment to masculinise or de-feminise their scores. This effect was not observed.

In conclusion, androgen administration to a group of hypogonadal and a group of eugonadal men had a general lack of effect on psychometric test battery scores, and the results oppose hypotheses generated from correlational studies which suggest that relationships exist between androgens and these test variabiles. However, it must be stated that these psychometric measures aim to measure relatively stable aspects of personality, and although short-term androgen treatment did not result in significant effects on test scores, the results do not entitle us to reject the hypothesis that, in the long term, alterations in circulating androgen levels may have an effect on certain aspects of non-sexual behaviour which, in turn, may be reflected in these psychometric test scores.

CHAPTER 9

ANDROGENS AND AGGRESSION IN MAN - A CONTROLLED CASE STUDY

9.1 INTRODUCTION

As reviewed in Chapter 1.8, a small number of studies have investigated the relationship between circulating androgen levels and aggressive behaviour in the eugonadal man, and have produced inconsistent results. A series of recent review articles on the subject (Benton, 1981; Brain, 1981; Herrman & Beach, 1976; Hinton, 1981; Kling, 1975; Rose, 1975; 1978; 1980; Rubin, 1982) agree in their criticisms of the studies carried out to date. In particular, unsatisfactory methods of measuring human aggression have often been employed (e.g. self-report questionnaires of doubtful validity) and single blood samples have often been used to determine an individual's androgen status. In spite of these methodological flaws, and the contradictory results supplied by these studies, the concensus of opinion suggests that the evidence is most convincing in respect of the relationship between androgens and aggression in behaviourally extreme populations, e.g. the violent rapist (Rada et al. 1976) and the violent long-term prisoner (Ehrenkranz et al. 1974).

Adequately controlled studies investigating the relationship between aggression and hypogonadism have been lacking. All the data in this area have been derived from follow-up interviews carried out with castrated sex offenders. In general the results suggest a major and dramatic effect of castration in acting to reduce the sexual interest and sexual activity of the offender. However, a significant proportion of castrates report no adverse influences in their sex drives, e.g. 10% (Cornu, 1973) and 18% (Langeluddeke, 1963). Of those interviewees who do report a diminution in sexual appetite, this could be interpreted as the expected response of an ex-prisoner who does not want to return to

jail. However, it is certainly true that very few castrated sex offenders return to prison.

At a first glance, recidivism rates of, for example, 2.2% (Sturup, 1968) appear very impressive; however, extreme caution is necessary when interpreting such figures:-

(a) As Heim and Hursch (1979) and Heim (1981) point out, there is very probably a large placebo effect following such radical genital surgery

(b) Following imprisonment alone, as few as 6% of rapists have been reported as being re-convicted for rape (Soothill, 1980)

In one of the most famous studies of the behavioural effects of castration in the human male, Bremer (1959) followed-up two hundred and forty-four men in Norway who had been castrated following repeated sexual offences. He reported that castration did have a general beneficial effect on aberrant sexual behaviour, but that the operation had no effect on aggression per se. Bremer concluded that castration is an inappropriate method of treatment for non-sexual aggressive behaviour in the human male.

Given the relative dearth of good evidence of an association between androgens and aggression in the human male, it is perhaps surprising how generally held the belief is that the two variables are causally related in man, e.g. "The evidence strongly suggests that aggression, hostility and fighting behaviour are all related to androgen level - the more androgen, the more aggressive the person!" (Eysenck and Wilson, 1979).

In the present chapter a controlled case study is reported of the behavioural effects of oral androgen replacement in a hypogonadal institutionalised man who had a previous history of aggressive

outbursts while receiving intramuscular testosterone injections.

9.2 MATERIALS AND METHODS

9.2.1 The Patient

D.B. was a 21 year old mentally retarded inmate of a hostel for the mentally handicapped run by Lothian Region Social Work Department. At the age of 7 years, he lost his left leg and both testes in a road traffic accident. At the age of 15 years he was treated for one year with the synthetic androgen fluoxymesterone. At the end of this course of treatment D.B. was clinically judged as having a rather acromegalic appearance, and in an effort to stimulate epiphyseal closure he was converted to high dosage testosterone treatment in the form of monthly Sustanon 250 injections, which allegedly precipitated frequent and relatively violent aggressive outbursts, and consequently the treatment was stopped.

D.B. was referred to Dr. John Bancroft and the author by the staff at the endocrine clinic of the Western General Hospital in Edinburgh. We were faced with the problem that the patient obviously required androgens to stimulate epiphyseal closure but that the administration of exogenous androgens appeared to provoke severe behavioural problems.

It was our opinion that if androgen treatment was in fact causing these aggressive outbursts, then Sustanon 250 injections may not be the most suitable form of replacement therapy, as we had previously observed that these intramuscular injections produce very high pharmacological levels of circulating testosterone, i.e. 400% of normal adult male levels for the few days following injection (see Fig. 4.1). We hypothesised that with a more gradual and stable method of testosterone administration, the androgenic effects necessary for bone

maturation may be provided without precipitating the bouts of aggressive behaviour that had previously been observed following the high dose testosterone injections.

A single-case study protocol was devised where the behavioural effects of gradually increasing the dose of testosterone undecanoate (T.U.) were assessed relying on blind daily ratings of D.B.'s behaviour by hostel staff members.

9.2.2 Behavioural Assessment

Satisfactory methods of measuring human aggression are lacking (see review by Edmunds and Kendrick, 1980). Inspection of published staff rating methods of patients behaviours (e.g. Hall, 1977; Shatin and Freed, 1955) revealed that none were suitable in this particular case as they did not deal specifically with aggressive behaviour. Self-report inventories which claim to measure aggression (e.g. Blackburn, 1974; Buss and Durkee, 1957) could not be used because of the patient's degree of mental retardation. The author therefore constructed a daily scale where hostel staff memebers, at their daily meetings, could assess D.B.'s behaviour over the previous 24 hours. A draft version of a simple seven point rating scale describing five aspects of behavioural functioning: Aggressive, Energetic, Sociable and Friendly, Irritable, and Cheerful and Happy was presented to the hostel staff and discussed. In general the daily rating scale met with their approval, but the majority felt that while D.B. had been receiving the high dose testosterone injections, he had been particularly prone to violent mood swings, and asked if some measure of this mood lability could be incorporated into the rating. In light of this suggestion an additional scale, Changeable or Up and Down was included. A copy of

the daily assessment form appears as Fig. 9.1.

D.B. was interviewed by the author prior to the study. He presented as a pleasant mentally slow young man. He denied having any degree of sexual interest or activity, but stated that he did have a girlfriend at the adult training centre he attended. When pressed, he stated that he did kiss and caress his girlfriend, but the impression that emerged was of a child-like, almost platonic relationship. D.B. denied ever having masturbated, or ever noticing any change in the size of his penis. Physical examination revealed a very small markedly deformed penis embedded in scar tissue, with the scrotum and testes absent.

D.B.'s parents and the hostel staff expressed concern over the possibility that androgen administration would stimulate sexual feelings which he would find difficult to cope with. They were informed that sexual counselling would be provided if required.

9.2.3 Design

For a baseline period of four weeks, hostel staff members completed the daily rating form assessing D.B.'s behaviour while receiving no androgens. The patient and the staff were then informed that D.B. would be given testosterone capsules, and that he would be administered a different dose every month for three months, but to ensure that the staff were not aware when he was on high or low doses of testosterone, every day for three months D.B. would be given four identical capsules, one, two or three of which would contain 40mg of active T.U., the remainder being made up with matched placebo. Two capsules were taken at 0800 hours, two at 1700 hours. Following the baseline month the dose was increased every month from 40 to

120 mg T.U./day, as described in Table 9.1 In addition to the daily staff ratings, D.B. was visited every month by the author who conducted an informal inverview to monitor any androgen mediated effects on sexuality.

In order to investigate the effects of T.U. administration on plasma testosterone levels, D.B. was brought into hospital for one day at the end of the study to participate in an absorption study. Blood samples were taken every 30 minutes, prior to, and six hours following oral ingestion of 80 mg T.U. Testosterone was assayed according to the method of Corker and Davidson (1978).

9.2.4 Analysis

The effect of varying the replacement dose of T.U. on D.B.'s behaviour, as assessed by hostel staff members, was analysed using repeated measures analysis of variance (ANOVAR).

9.3 RESULTS

9.3.1 Behavioural Results

Table 9.2 reveals that increasing the replacement dose of T.U. had no effect on any of the daily ratings of behaviour as assessed by hostel staff members. In addition, at the monthly informal interviews conducted by the author, D.B. denied any increase in sexual feelings. (In fact, he repeatedly stated that the T.U. capsules were "just like sweets", i.e. he felt that they were completely without behavioural effect).

9.3.2 Endocrine Results

As can be seen (Fig. 9.2) oral ingestion of 80 mg T.U. led to circulating testosterone levels which were maintained within the normal adult male range for several hours.

TABLE 9.1

T.U. DOSAGE REGIME

Month	0800 hr. dose	1700 hr. dose
1 (Baseline)	-	-
2 (40 mg/day)	1 40 mg capsule 1 placebo capsule	2 x placebo capsules
3 (80 mg/day)	"	1 40 mg capsule 1 placebo capsule
4 (120 mg/day)	2 x 40 mg capsules	"

TABLE 9.2

STAFF RATINGS OF AGGRESSIVE BEHAVIOURS OF A HYPOGONADAL MAN WHILE RECEIVING NO ANDROGEN TREATMENT AND ON THREE MONTHS OF INCREASING REPLACEMENT DOSAGE OF TESTOSTERONE UNDECANOATE

	Mean (± S.D.) Staff Rating Per Monthly Treatment Period				
Behaviour	Basal	T.U.40	T.U.80	T.U.160	ANOVAR
Energetic	4.1(1.9)	3.6(1.1)	3.5(1.1)	4.5(1.0)	F=2.53, N.S.
Irritable	2.3(1.2)	2.1(1.4)	2.4(1.6)	2.2(1.7)	F=0.03, N.S.
Aggressive	1.8(1.9)	1.4(1.1)	1.9(1.3)	2.2(1.8)	F=0.72, N.S.
Cheerful	5.2(1.5)	4.9(1.2)	4.1(1.4)	4.6(1.7)	F=1.53, N.S.
Sociable	5.0(1.6)	4.8(1.3)	4.0(1.4)	4.5(1.9)	F=1.67, N.S.
Changeable	1.7(1.0)	2.4(1.8)	1.7(1.2)	1.7(1.2)	F=0.91, N.S.

FIGURE 9.1

Daily Assessors Rating Form for D.B. Date .....

Please indicate on the scales below, (by circling the appropriate number) how D.B. has behaved today.

Cheerful & Happy

1 2 3 4 5 6 7

Aggressive

1 2 3 4 5 6 7

Energetic

1 2 3 4 5 6 7

Sociable & Friendly

1 2 3 4 5 6 7

Irritable

1 2 3 4 5 6 7

Changeable or Up and Down

1 2 3 4 5 6 7

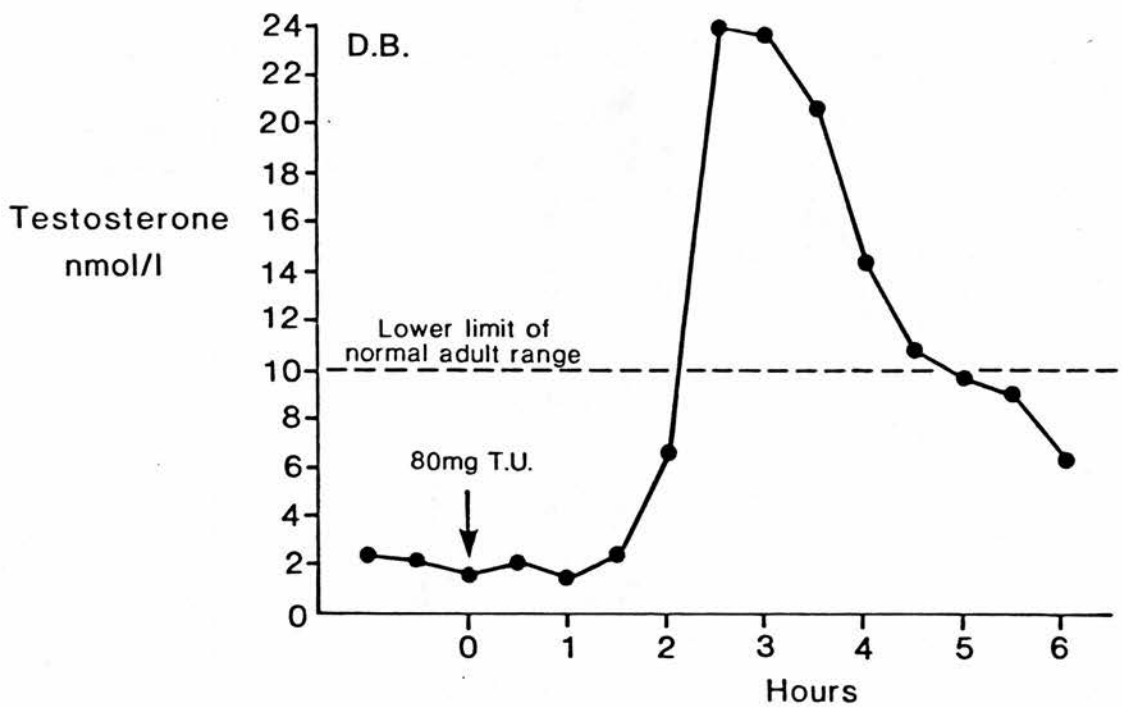

FIGURE 9.2

The effect of oral ingestion of 80 mg T.U. on circulating testosterone levels in a hypogonadal man.

9.4 DISCUSSION

In this particular hypogonadal man we have managed to provide a satisfactory degree of testosterone replacement without provoking the aggressive outbursts which had been reported while D.B. was receiving treatment with Sustanon 250 injections. There are four possible reasons for this differential behavioural response to the different androgen preparations:-

(1) The aggressive outbursts which occurred while D.B. was receiving the Sustanon injections may have been coincidental rather than causally related. The bouts of aggression could possibly have been more due to inter-personal conflicts with particular patients or staff at that time, and may have had nothing to do with the treatment.

(2) The staff may have been biased in their behavioural reports as they were aware that D.B. was being given high dosage "male hormone" injections (although no such reports were made previously while D.B. was being treated with the oral fluoxymesterone).

(3) The aggressive outbursts were a direct result of the very high testosterone levels which result following Sustanon injections. These massive swings in circulating testosterone levels may have acted on the brain to make D.B. more predisposed to aggressive outbursts. While receiving T.U., plasma levels of testosterone were kept within the normal adult male range, i.e. this mode of androgen replacement resulted in an androgen profile more similar to that of the normal man.

(4) The aggressive outbursts brought about as a result of the Sustanon injections could have been indirectly due to the elevated testosterone levels which were then aromatized to oestradiol which in turn

stimulated "aggression centres" in the central nervous system. (Many of the organisational effects of androgens on the brain are thought to be brought about via neural aromatization to oestradiol, Gorski and Jacobson, 1982). T.U. replacement did not have this effect as T.U. administration leads to a greater proportional elevation of systemic non-aromatizable DHT compared with testosterone (Skakkebaek et al. 1981). (Most of the somatic effects of androgens have been shown to depend on DHT, Mainwaring, 1977).

It is possible that if androgens have a stimulatory effect on aggressive behaviour in the human male, the mechanism of action is via aromatization of testosterone to oestradiol. This hypothesis would account for the observation that during the one year of treatment with the non-aromatizable synthetic androgen, fluoxymesterone, hostel staff did not report aggressive outbursts (see Section 9.2.1).

This explanation of the differential behavioural effects of T.U. and Sustanon is obviously rather speculative. Preliminary data on the relative effects of testosterone, oestradiol and DHT on aggressive behaviour in animals have been presented, e.g. in the mouse (Finney and Erpino, 1976) and in the deer (Fletcher, 1978) but as yet details of the relative contributions of testosterone, oestradiol and DHT in the regulation of human aggressive behaviour are lacking.

The results of the present case study demonstrate that gradually increasing the dose of T.U. did not act to precipitate bouts of aggressive behaviour in a hypogonadal man who had previously been reported as acting very aggressively while receiving high dose testosterone injections. Possible reasons for these different behavioural results with the different androgen preparations have been

suggested. Gradually increasing the dose of T.U. may offer particular advantages over injectable preparations such as Sustanon where the somatic effects of the androgen are of primary importance and where alternative androgen preparations have produced unwanted behavioural side-effects such as hyperaggression.

Finally, it is important to remember how poor the evidence is of an androgen involvement in human aggression, and how few properly controlled studies have been carried out. In the studies described in this thesis, no evidence was produced to suggest that androgen administration acted to stimulate aggressive behaviour in man. In fact in the hypogonadal study (Chapter 3), the hypogonadal men rated themselves as feeling less aggressive while receiving the highest replacement doses of testosterone undecanoate. In the eugonadal studies of the behavioural effects of androgen administration in men complaining of loss of libido (Chapter 5) and erectile dysfunction (Chapter 6), daily self-ratings of irritability and aggression were not significantly different when placebo treatment was compared with high dosage testosterone treatment.

Eysenck's psychoticism or P scale (Eysenck and Eysenck, 1975) has been proposed as an indirect measure of human aggressiveness (Edmunds and Kendrick, 1980). Again, in the hypogonadal and eugonadal studies androgen administration had no effect on P scores (Chapter 8).

Thus the results reported in this thesis fail to provide any evidence to support clinical impressions that androgen administration provokes aggressive outbursts in man (Sands and Chamberlain, 1957; Strauss et al. 1957). However, controlled double blind studies are urgently required which carefully monitor aggressive behaviour

following androgen administration in the hypogonadal man. Until such studies are carried out, the question of a relationship between androgens and human aggression remains unanswered.

CHAPTER 10

GENERAL DISCUSSION

10.1 INTRODUCTION

In this final chapter the relationship between androgens and behaviour in man is reviewed in light of the experimental findings presented in this thesis. This discussion is presented in four sections: Androgens and Erectile Function, Androgens and Sexual Interest, Androgens and Mood and Personality, and Methodological Issues arising from the Research Presented.

10.2 ANDROGENS AND ERECTILE FUNCTION

Bancroft (1980) proposed that the primary behavioural action of androgen in man is to stimulate sexual appetite, and that erectile function *per se* is relatively independent of androgen status. Evidence to support this hypothesis was presented by Bancroft & Wu (1983) and Kwan *et al*. (1983) who reported that erectile response to erotic film was unaffected by androgen replacement and withdrawal in the hypogonadal man. (However, Bancroft & Wu (1983) made the fascinating observation that erections in response to erotic fantasy were markedly reduced following androgen withdrawal).

Davidson *et al*. (1979) claimed that the reported frequency of erections on waking in the hypogonadal man was clearly stimulated by androgen replacement therapy. Similar data was supplied by Salmimies *et al*. (1982). In the hypogonadal study described in Chapter 3, the reported frequency of morning erections was demonstrated to vary in a clear dose-dependent manner with androgen replacement. Similarly in Chapter 7 direct measurement of nocturnal erectile response revealed that hypogonadal men display diminished nocturnal erectile function which improves following androgen replacement therapy. Kwan *et al*. (1983) also reported this stimulatory action of androgen replacement on

nocturnal erectile function in the hypogonadal man.

We are therefore faced with this contrary data, i.e. that the reported incidence of morning erections (residual nocturnal erections), directly measured nocturnal erections, and erections in response to erotic fantasy all appear to be clearly androgen dependent, whereas erections in response to erotic film are relatively unaffected by androgen replacement and withdrawal. It is possible that erections in response to erotic fantasy and nocturnal erectile responses differ qualitatively from erections in response to erotic film in that the former are generated in response to an "internal" stimulus as opposed to the external film stimulus, i.e. the central cognitive stimulus for erection in man may be androgen dependent, whereas the hypogonadal man retains the ability to produce erections in response to a powerful and sexually stimulating external stimulus. This hypothesis would account for the observation that some castrate men retain the ability to produce erections during sexual contact (Heim, 1981). It is important to note that this hypothesised central action of androgens was shown not to be (as Bancroft, 1980 suggested) the result of a general stimulatory effect of androgens on visuo-spatial ability (See Chapter 8).

In their recent attempts to replicate the Bancroft & Wu (1983) study, Kwan et al. (1983) reported that the ability of hypogonadal men to produce erections in response to erotic fantasy was relatively unaffected by androgen replacement. However, careful reading of the Kwan et al. (1983) paper reveals that three out of their six hypogonadal subjects produced very poor erections in respose to erotic fantasy, and two out of these three men demonstrated an improved

response to fantasy following testosterone treatment. Therefore the Kwan et al. (1983) results are not totally contrary to those supplied by Bancroft & Wu (1983).

The results of two recent studies using eugonadal men as subjects provide data which is difficult to reconcile with the Bancroft & Wu (1983) hypothesis, i.e. that circulating androgen levels are not related to erectile response to erotic films. Lange et al. (1980) and Rubin et al. (1979) both reported that circulating testosterone levels were in fact highly correlated with latency to full erection in response to erotic film. However, in general, studies investigating the efficacy of androgen administration in the treatment of erectile dysfunction have produced negative results. As was suggested in Chapter 1.4.2, it is possible that these negative results were due to the fact that the androgen administration did not result in an increase in circulating androgen levels due to the eugonadal homeostatic mechanisms which operate. In Chapter 4, we managed to overcome these homeostatic mechanisms using frequent intramuscular depot injections of testosterone. However, this method of androgen administration was shown to be ineffective in the treatment of erectile dysfunction in the eugonadal man (Chapter 6).

At this point in time the issue of the relationship between androgens and erotically induced erections remains unresolved; however, there is good evidence to support the hypothesis that nocturnal erectile function in man is androgen dependent.

10.3 ANDROGENS AND SEXUAL INTEREST

Several investigators have proposed that androgens act to stimulate sexual interest or libido in man (e.g. Money, 1961;

Bancroft, 1980; Davidson et al. 1982) although until very recently few studies had attempted to directly test this hypothesis. In 1980 Luisi & Franchi presented data in support of the hypothesis. These authors reported that androgen administered to hypogonadal men acted to significantly increase their level of self-rated libido. Similar results were presented by Skakkebaek et al. (1981). In their study the frequency of sexual thoughts and sexual excitement associated with these thoughts of a group of hypogonadal men were clearly stimulated by androgen administration as opposed to placebo treatment. In the hypogonadal study described in Chapter 3, frequency of sexual thoughts and sexual excitement associated with these thoughts were shown to vary in a clear dose dependent manner with androgen replacement. This result confirms the findings of Salmimies et al. (1982) who reported that "sexual drive" increased with androgen replacement dose. Similarly Kwan et al. (1983) reported that "sexual feelings" displayed a progressive increase following blind injections of placebo and increasing doses of testosterone.

Thus the evidence derived from studies carried out on the hypogonadal man strongly support the hypothesis that androgens have a major stimulatory effect on sexual interest, and that this effect is a dose dependent one.

When we turn to look at the relationship between androgens and sexual interest in the eugonadal man, the picture is less clear. Previous investigators have generally failed to find any relationship between circulating testosterone levels and sexual interest or activity in the normal man (e.g. Brown et al. 1978) and androgen treatment is generally considered to be unhelpful in the treatment of sexual

dysfunction in the eugonadal male. However in Chapter 5 a study is reported where testosterone injections were shown to be superior to placebo in the treatment of eugonadal men complaining specifically of low sexual interest. This effect was apparent both when self-rating and interview ratings of sexual interest were analysed. This is an important finding, and if replicated could prove to have far reaching consequences in the field of sex therapy. However, in only three out of the ten men studied did this increase in sexual appetite constitute a sufficient therapeutic response, i.e. in terms of increased sexual activity. It was proposed that in most of the subjects other factors, e.g. communication difficulties, resentment, hostility, etc. prevented this increase in sexual appetite being reflected in an increased frequency of the sexual activity of the couple. A model was proposed linking marital dysfunction, stress, reduced androgens, decreased sexual interest and a decreased frequency of sexual activity in a self-perpetuating "vicious circle" (see Fig. 5.3). The author suggested that this vicious circle could be broken in a number of ways, e.g. androgen treatment for the man with low sexual interest coupled with psycho-sexual counselling for the couple where the emphasis would be placed upon improving the communication between the couple and, if necessary, encouraging the female to take the sexual initiative.

Although the results of the hypogonadal study (Chapter 3) and the results of the study on the eugonadal men complaining of loss of sexual interest (Chapter 5) support the hypothesis that androgens have a stimulatory effect on sexual interest, in the study described in Chapter 6 a group of eugonadal men complaining of erectile dysfunction

with no loss of interest in sex were treated with depot testosterone injections, and androgen administration was shown to be entirely without behavioural effect. In accounting for this differential effect of androgen administration in the different patient groups, the author proposed that (a) the erectile dysfunction group had a relatively "normal" degree of interest in sex and therefore had less scope for improvement, and (b) that although the evidence suggests that androgens stimulate sexual interest in the majority of hypogonadal men, there may be an optimal circulating theshold testosterone level in man, any alteration above this theshold having no behavioural effect. It is proposed that this optimal level of circulating testosterone may not be an absolute one in terms of nmol/l (as has been previously suggested, Pirke & Kockott, 1982) but is highly variable across individuals. This hypothesis would account for the observation that some hypogonadal men display a relatively normal degree of sexual interest and activity despite having very low circulating testosterone levels (e.g. Salmimies et al. 1982) and would also account for the stimulatory effect of the testosterone injections in the low libido eugonadal men (Chapter 5) who had a mean basal testosterone level which was greater than 20 nmol/l.

Further studies are necessary to determine exactly which facets of sexual functioning in the adult human male are androgen dependent; however the results of the studies described in this thesis suggest that sexual interest and nocturnal erectile function are dependent on an adequate level of circulating androgen.

10.4 ANDROGENS AND MOOD AND PERSONALITY

10.4.1 Androgens and Mood

Studies carried out to date investigating the relationship between androgen replacement and mood in the hypogonadal man have produced inconsistent results. Luisi & Franchi (1980) claimed that "mental state" was markedly improved following androgen replacement. Similarly Skakkebaek et al. (1981) reported that fatigue and tension/anxiety were reduced and vigour increased during active treatment compared with placebo. Davidson et al. (1979) and Salmimies et al. (1982) however reported a lack of effect of testosterone replacement on mood. In the hypogonadal study described in Chapter 3, the effects of androgen replacement on mood were generally modest, but the hypogonadal men did rate themselves as feeling less tense and anxious, changeable, and irritable while taking the higher doses of testosterone undecanoate. However, neither the eugonadal men complaining of reduced sexual interest (Chapter 5) nor the eugonadal men complaining of erectile dysfunction (Chapter 6) reported any effect of high dosage testosterone administration on mood state.

It is possible that the improvements in mood state that have been reported in the literature following androgen treatment for hypogonadism are a result of the general improvement in sexual functioning, i.e. anxiety and general negative mood states in the untreated hypogonadal man may be partially due to the very severe sexual difficulties associated with hypogonadism and would thus tend to improve following the beneficial effects of testosterone therapy on sexual functioning.

This hypothesis is in direct opposition to that proposed by Kinsey et al. (1953), i.e. that androgens act primarily on general metabolism and mood and only secondarily on sexual functioning. Further studies closely analysing the temporal changes in sexual functioning and mood following androgen replacement in the hypogonadal man are required to determine which aspects of behavioural functioning are affected first.

10.4.2 Androgens and Personality Measures

Several investigators have proposed that scores on certain personality measures are related to circulating androgen levels in the eugonadal man. To date, all the evidence in support of this hypothesis has been derived from correlational studies equating mean circulating testosterone level with psychometric test scores (See Chapter 1.6-1.7). In the studies described in this thesis experimental elevation of circulating androgen levels resulted in a general lack of effect on psychometric test scores in both the hypogonadal and eugonadal groups of men (Chapter 8). No support was therefore drawn for hypotheses which had suggested that sensation seeking behaviour, spatial ability and scores on Eysenck's P scale were related to androgen levels. However, these negative results must be qualified in that the psychometric tests claim to measure relatively stable dimensions of personality. It could therefore be argued that these test scores would be unlikely to show significant changes following relatively short-term androgen treatment. In reply, it is important to note that Kaiser et al. (1978) reported significant effects on a variety of personality tests following five weeks treatment with mesterolone using a group of elderly men as subjects. (The Kaiser et al. (1978) result is surprising given that Luisi & Franchi (1980) found mesterolone to be

ineffective and testosterone undecanoate highly efficacious in the treatment of male hypogonadism, suggesting that mesterolone is a behaviourally weak androgenic preparation).

10.5 METHODOLOGICAL ISSUES ARISING FROM THE RESEARCH PRESENTED

10.5.1 Free Steroid Estimation

An important methodological point which emerged from the studies carried out in the eugonadal man was the difficulty involved in estimating the actual concentration of free androgen in the plasma, i.e. the fraction of bio-active hormone that is available at the receptor (Bergink et al. 1981). One relatively recent approach which would appear to offer a distinct advantage over labour intensive assay methods which estimate the free steroid concentration in the plasma is the method of salivary steroid assessment (Walker, 1983). These new asays measure the amount of steroid which passes from the systemic circulation into the saliva. Salivary steroid concentrations have been shown to correlate very highly with plasma estimates of free steroid, obtained using a variety of laborious methods (Riad-Fahmy et al. 1982). In future studies, steroid assay of salivary samples may offer a simpler, more direct and more accurate assessment of bio-active androgen status in the human male and female. Salivary sampling also removes the stress experienced by some individuals prior to and during venepuncture. (It is important to note that venepuncture itself may have an effect on the neuro-endocrine system in man, e.g. Lincoln, 1974).

10.5.2 SHBG Estimation Following Testosterone Undecanoate Administration

A study is described in Appendix II which demonstrates that following administration of testosterone undecanoate (T.U.), plasma DHT levels become elevated and this elevation in DHT acts to interfere with the accuracy of the SHBG assay by binding to the SHBG molecule, leaving fewer binding sites on the protein to be filled by the tritiated DHT used in the SHBG assay. It is therefore recommended that in future studies samples from men receiving T.U. have steroids removed from plasma samples prior to SHBG estimation when the DHT-binding assay is to be used.

10.5.3 Variability in Absorption of Testosterone Undecanoate

Recent evidence (Cantrill et al. 1983; Schurmeyer et al. 1983) has demonstrated that individuals vary in the rate at which they absorb testosterone undecanoate. (This variability in T.U. absorption rates was confirmed in a small study described in Appendix III). In the studies described in Chapters 3 and 4 it is probable that our fixed single post-dose blood sampling regime was inadequate for assessing these variable effects of T.U. ingestion on circulating androgen levels. In future studies using T.U., absorption curves involving frequent post-dose blood sampling will have to be carried out for each individual in order to pick up these variable peaks in plasma testosterone levels that occur following T.U. administration. It is important to note that these absorption rates may vary both inter- and intra-individually.

10.5.4 Methods of Raising Circulating Testosterone Levels in Eugonadal Men

In Chapters 4,5, and 6 it was demonstrated that intramuscular Sustanon injections proved to be a satisfactory method for increasing circulating testosterone levels in the eugonadal man. However, this experimentally induced elevation in systemic testosterone level was not sustained; for the few few days following injection plasma testosterone levels were massively elevated (i.e. 400% of the normal adult male levels), thereafter testosterone levels fell back to basal levels over a two week period. (Oral administration of T.U. did not appear to overcome the eugonadal homeostatic control mechanisms, and plasma testosterone levels were not significantly affected (Chapter 4). However, as stated above, the single post-dose blood sampling regime employed was probably inadequate for assessing the effect of T.U. ingestion on plasma testosterone levels, given the variability that exists in T.U. absorption rates).

It is possible that sustained elevations in circulating testosterone levels without these wild supraphysiological swings could be brought about using silastic testosterone implants. However the effect of testosterone implants on the endocrinology of the eugonadal man awaits experimental investigation.

10.5.5 Behavioural Measurement

10.5.5.1 Assessment of Sexual Behaviour

All of the studies reported in this thesis can be criticised in that the effect of androgen administration on the sexual behaviour of men has been investigated with no formal assessment incorporating the sexual partner. In many instances, this was unavoidable as the female

partners refused to attend for psycho-sexual counselling and the man was forced to seek help alone. However, in future studies, every effort should be made to include both partners in the experimental design.

It is also important to stress the need for daily assessments of sexual behaviour, i.e. diaries. While some investigators have claimed that retrospective (recall) data is a valid form of behavioural assessment (e.g. Spanier, 1977), recent evidence comparing daily records with monthly estimates of sexual behaviour have shown that, for example, monthly estimates of frequency of morning erections correlate poorly with daily records (Reading et al. 1982; Reading, 1983).

10.5.5.2 Assessment of Aggressive Behaviour

There has been relatively little research carried out on the relationship between androgens and human aggression. In the studies that have been published, too much reliance has been placed upon self-report questionnaires such as the Buss-Durkee Hostility Inventory (Buss and Durkee, 1957), even though scores on these inventories have been shown not to correlate with observed aggressive behaviour (Rose, 1975). In the opinion of the present author, future studies should attempt to utilise observer ratings of aggressive behaviour. Using highly aggressive subjects (e.g. violent incarcerated criminals) the observer rating method described by Ehrenkranz et al. (1974) would appear to be an approach worthy of replication. In less behaviourally extreme samples, social taboos on the expression of aggressive behaviour make it difficult to directly observe human aggression. However studies such as that by Scaramella & Brown (1978) which utilise sport as an area of human activity where societal constraints on the

expression of aggressive behaviour are temporarily lifted (and in some instances aggressive behaviour is actively encouraged) would again appear to be an approach worthy of further investigation.

10.5.6 Surgically Induced Hypogonadism - The Question of Pre-Operative Counselling

In discussions with the hypogonadal subjects described in Chapter 3, several men demonstrated a lack of knowledge concerning the consequences of their condition. To take an example, one castrate man asked if he would be able to make his wife pregnant. He was under the impression that his fertility would be reduced but had not discussed the topic with a clinician. The same hypogonadal patient told the author that after being given his pre-medication prior to his bilateral orchidectomy, the surgeon asked him if he would be interested in having prostheses inserted. The patient did not know what a prosthesis was.

It is possible that these were isolated incidents, but it would surely be a good routine policy to have detailed pre-operative counselling sessions with such patients, where the likely physiological and psychological effects of the operation could be explained. Also, the question of prosthetic replacement and the various alternative forms of androgen replacement could be discussed.

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APPENDIX I

THE EFFECTS OF BROMOCRIPTINE ON THE SEXUAL BEHAVIOUR OF A HYPERPROLACTINAEMIC MAN: A CONTROLLED CASE STUDY*

*This study was carried out in collaboration with Dr. J. Bancroft, Dr. A. McNeilly and Professor R. Shaw.

The association between hyperprolactinaemia and sexual dysfunction in men is now well established (Carter et al. 1978; Perryman & Thorner, 1981). Improvement in sexual function has been widely reported to follow treatment with bromocriptine and the consequent reduction in prolactin levels (Franks et al. 1978; Nagulesparen et al.1978). As yet there are no controlled studies of these associations or treatment effects. It therefore remains uncertain which aspects of male sexuality are primarily affected by the hyperprolactinaemia. Is it sexual appetite or does the raised prolactin have a direct effect on erectile function?

The case study reported here throws some light on this issue.

CASE HISTORY

The patient (M.J.) is a 44 year old engineer who presented in 1977 with his wife at a sexual problems clinic, complaining of loss of sexual interest and erectile impotence. At that stage, he and his wife were treated in a study evaluating testosterone treatment in comparison with placebo, each being combined with counselling for the couple. M.J. received placebo together with counselling and by the end of treatment there had been considerable improvement. His erectile problems had disappeared, and whereas there had been a slight increase in his spontaneous sexual interest, the important change was in his wife's attitude. Previously, she had been reluctant to initiate sexual activity. As a result of the counselling she was quite prepared to do so and they were both able to enjoy the lovemaking that resulted.

Six months after treatment, this improvement had been maintained and after many years of infertility she had become pregnant with twins.

Serial blood samples from M.J. had been taken before treatment and again six months after treatment ended. As the response to treatment was so satisfactory, no priority was given to completing all the hormone assays. Three years later it was found that both prior to treatment and at follow-up he had hyperprolactinaemia (4670 and 4756 mU/L respectively). His mean testosterone levels on these two occasions were normal at 20.7 and 16.5 nMol/L. As a result of these hormone measurements, he was contacted again, when he reported that his sexual relationship had remained satisfactory, though his spontaneous sexual interest was still somewhat low. His plasma prolactin level was found to be still high at 5721 mU/L with his testosterone at 15 nMol/L. Further investigations were then carried out. Skull X-ray and CAT scan demonstrated slight asymmetry of the fossa floor, but no increase in volume. Tissue density within the fossa was normal with no change by contrast injection and no abnormal tissue formation in the suprasellar region. Combined pituitary function tests showed normal GH, TSH, LH, FSH and cortisol responses. Prolactin levels increased from a basal of 4790 mU/L to 6420 mU/L at 30 min following 200 ug TRH. There was therefore no evidence of a pituitary tumour. Seminal analysis showed a total sperm count of 468 x 10^6. He was advised to have treatment to lower his prolactin levels and agreed to participate in a double blind controlled evaluation of bromocriptine and placebo (Study 1). Following this he was prescribed bromocriptine and followed up a year later. Due to a misunderstanding he had stopped taking bromocriptine some months previously. Both his sexual interest and prolactin levels had returned to their previous level, though otherwise sexual function

was still satisfactory. He again agreed to undergo a double blind comparison of bromocriptine and placebo (Study II).

METHOD

Study 1

For a period of seven months, M.J. completed a daily diary indicating the incidence of sexual activity, whether initiated by self, partner or mutually, presence or absence of morning erections and the degree of sexual interest (See Appendix IV). Weekly blood samples for endocrine assessment were taken throughout this period and were subjected to established assays of testosterone (Corker & Davidson, 1978), SHBG (Anderson et al. 1976), prolactin (McNeilly & Hagen, 1974), LH and FSH (Hunter & Bennie, 1979). The presence of different molecular forms of prolactin was investigated by chromatographic separation of plasma samples before and after bromocriptine treatment. Samples were passed down a Sephadex G-100 (1 x 60 cm) column, using the method described by Hagen & McNeilly (1975). All samples were measured in a single assay.

The first six weeks were used as baseline, with no treatment given. For the next six weeks, M.J. was administered testosterone (Sustanon 250 injections at three weekly intervals). He was then started on bromocriptine, with gradually increasing dosage to assess his prolactin response and the appropriate dosage to use. His prolactin levels rapidly dropped to sub-normal levels on the dosage of 10 mg bromocriptine per day (55 mU/L) and he experienced mild gastro-intestinal side-effects. A dosage of 7.5 mg, free from side effects, was therefore selected for the double blind placebo

comparison. This maintained plasma prolactin at a mean of 259 ± 84 mU/L. Thereafter he received treatment according to a double-blind schedule; 5 weeks on bromocriptine, 5 weeks on placebo and 5 weeks bromocriptine.

Study II

The same measures of sexual activity and interest were used and blood samples were taken at two weekly intervals. After a two week baseline period of no treatment, he received two weeks of placebo and six weeks of bromocriptine (7.5 mg daily), in a double blind fashion.

In both studies, sexual interest scores during placebo and bromocriptine administration were compared using t-tests after logarithmic transformation.

RESULTS

The mean levels of sexual interest and sexual activity, together with the proportion of sexual acts initiated by the subject and the proportion of days in which M.J. experienced waking erections, during the baseline period, Sustanon administration and the double blind administration of bromocriptine and placebo for Studies I and II are shown in Table I.1.

Self-rated sexual interest was significantly higher whilst on bromocriptine than on placebo in both studies. There was no difference in this measure between the baseline and Sustanon periods in the first study. Frequency of sexual activity did not change significantly throughout either study, although there was a tendency for the proportion of acts initiated by M.J. to be higher during both Sustanon and bromocriptine treatment (especially in Study II). No erectile

TABLE I.1

SEXUAL INTEREST AND BEHAVIOUR IN A HYPERPROLACTINAEMIC MAN DURING VARIOUS STAGES OF TREATMENT

	Sexual Interest (0-100)		Sexual Activity per week		Activity initiated by Subject		Waking Erection % of mornings	
	Study I	Study II	Study I	Study II	Study I	Study II	Study I	Study II
	$\bar{x}$ (s.d.)	$\bar{x}$ (s.d.)	$\bar{x}$ (s.d.)	$\bar{x}$ (s.d.)	%	%	%	%
Baseline	13.0 (4.1)	9.2 (4.2)	1.0 (1.3)	1.5 (0.7)	33	0	17	43
Sustanon	11.7 (6.9)	-	1.5 (1.0)	-	44	-	37	-
Placebo	10.1 (4.3)	9.8 (3.3)	1.5 (1.4)	1.5 (0.7)	33	0	34	31
Bromocriptine	18.1** (10.1)	16.7*** (5.7)	1.0 (1.5)	1.7 (0.8)	50	50	30	54

Comparison with placebo **p = < 0.01
***p = < 0.001

TABLE I.2

PLASMA HORMONE LEVELS IN A HYPERPROLACTINAEMIC MAN DURING VARIOUS STAGES OF TREATMENT: STUDY I

Treatment		Prolactin mU/L	Testosterone nMol/L	SHBG nMol/l	LH U/L	FSH U/L
Baseline	Mean (s.d.)	4999 (429)	17.8 (2.6)	25.5 25.4	5.7	2.6
Sustanon	Mean (s.d.)	5134 (650)	22.2 (9.7)	23.6 (3.7)	2.9 (1.8)	1.7 (0.7)
Placebo	Mean (s.d.)	2095 (1159)	20.8 (5.2)	29.2 (4.9)	4.4 (0.5)	2.9 (0.3)
Bromocriptine	Mean (s.d.)	259 (84)	21.2 (2.8)	27.7 (5.3)	4.5 (0.6)	3.0 (0.5)

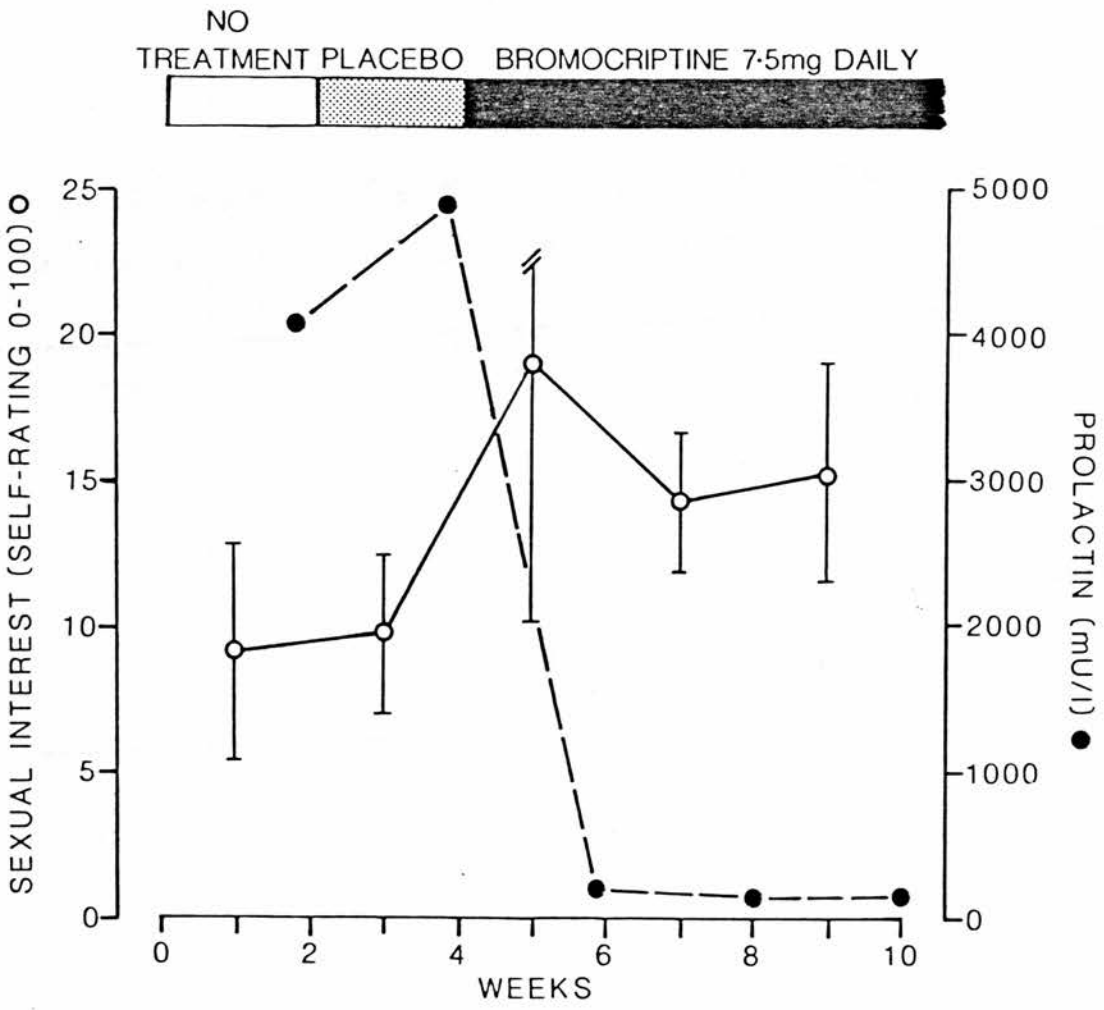


FIGURE I.1

The effect of bromocriptine and placebo treatment on sexual interest (frequency of sexual thoughts) and plasma prolactin levels in a hyperprolactinaemic man.

difficulties were reported at any stage and there were no differences in the incidence of morning erections. The change in sexual interest in Study II is shown in Fig. I.1.

ENDOCRINE CHANGES

Mean levels of prolactin, testosterone, SHBG, LH and FSH during each of the treatment periods in Study I are shown in Table I.2. Prolactin levels during Study II are shown in Fig. I.1. Prolactin did not change during Sustanon administration, but dropped to normal levels during bromocriptine therapy. On placebo, levels rose but did not reach those prior to treatment. The percentage of "big" prolactin prior to and during the bromocriptine phase was 15.7% and 66.3% respectively (Study I).

DISCUSSION

This case study is informative for a number of reasons. It shows that erectile impotence associated with hyperprolactinaemia can be treated by psychological means, an observation made fortuitously because of the delay in measuring the prolactin. This suggests that the erectile failure was a psychological reaction to the loss of sexual interest in a couple where the man was expected to take the initiative. The main effect of counselling was to alter this expectation so that the male partner did not feel under pressure to initiate and became able to respond normally when his wife did so. Once the improvement occurred, normal sexual function persisted over several years in spite of continuing very high prolactin levels and low levels of spontaneous sexual interest.

The residual effect of the hyperprolactinaemia was a somewhat reduced level of sexual interest as indicated by the statistically significant effect of bromocriptine treatment in increasing sexual interest as compared with placebo. Whilst there was no increase in the incidence of sexual activity, treatment did result in an increase in the number of acts initiated by the subject. In both studies, there was a large transient increase in sexual interest when first starting on bromocriptine. Why this level of response was not maintained is not clear, but it is not unusual in treating hypogonadal men with testosterone replacement to obtain an initial marked increase in sexual interest before a more moderate stable state is maintained.

This controlled case study validates the uncontrolled observations reported by Schwartz et al (1982). One hundred and thirty six men had received psychotherapy for sexual dysfunction at the Masters & Johnson Instititue. Blood samples had been taken prior to therapy but prolactin was not measured until some years later when 8 men (6%) were found to have substantial hyperprolactinaemia due to pituitary adenomas. Contact with these men after treatment was limited to the telephone, but all had reported improvement in sexual function (especially erection) following psychotherapy and a further improvement in sexual interest after the hyperprolactinaemia had been treated with bromocriptine.

The main difference was that all the eight hyperprolactinaemic men reported by Schwartz et al (1982) had low levels of testosterone. In our case this was not so, though his levels were in the lower part of the normal range. He showed no significant increase in testosterone

during bromocriptine therapy however and this, together with the lack of response to Sustanon, made it unlikely that his loss of sexual interest was the direct result of testosterone deficiency. Many hyperprolactinaemic men do have testosterone levels in the hypogonadal range (Perryman & Thorner, 1981; Legros et al. 1980) and in such cases androgen deficiency could be adding to the behavioural effects of hyperprolactinaemia.

Hypogonadism of Hyperprolactinaemia - Mechanism of Effect

Several mechanisms have been proposed to account for this association between elevated prolactin and reduced testosterone levels. Fonzo et al. (1977) suggest a direct effect of prolactin on the testis; other hypotheses include: a prolactin mediated disorder of the negative feedback to the hypothalamic-pituitary axis (Carter et al. 1978; Franks, 1981; McNeilly, Sharpe & Fraser, 1983); a reduced turnover of testosterone to dihydrotestosterone presumably mediated via 5 α -reductase inhibition (Magrini et al. 1976; Legros et al. 1980); and recently Vermeulen et al. (1982) proposed a reduction in the SHBG level in the hyperprolactinaemic man leading to increased metabolic clearance of testosterone and hence a reduced free testosterone level in the blood. In the face of these differing hypotheses, Perryman and Thorner (1981) conclude, "the data are confusing and inconsistent, and no conclusion is possible at the present time".

Hyperprolactinaemia and Sexual Dysfunction

Miller et al. (1980) point out a contradiction in the literature concerning the incidence of hyperprolactinaemic men complaining of "impotence" at presentation. Carter et al. (1980) reported that 20/22

of their hyperprolactinaemic men presented with reduced libido and/or erectile dysfunction, whereas Thorner et al. (1977) stated that only 1/17 of their hyperprolactinaemic men presented with the isolated complaint of impotence. In equating these findings Miller et al. (1980) state "The disparity between these two groups of patients may be owing to the confusion arising between impotence and loss of libido". The present author would like to endorse this point put forward by Miller et al. (1980) and to go further and suggest that erectile mechanisms per se may not be influenced directly by prolactin levels. In our case M.J. showed no differences in percentage of morning erections between bromocriptine and placebo treatments and at no time during the study did he report experiencing any erectile difficulties. The present author would propose that the primary behavioural effect of hyperprolactinaemia in men is one of diminution of sexual appetite, with erectile failure, when it occurs, being a psychological reaction to this loss. This hypothesis may account for the contrary data in the literature concerning sexual problems at presentation in hyperprolactinaemic men.

Erectile Impotence and Prolactin Levels

A controversy exists regarding the incidence of men complaining of impotence who have elevated prolactin levels. Rao et al. (1981) claimed that 15/25 men presenting with impotence had elevated prolactin levels ($\geq$800 mU/l) while Ambrosi et al. (1977) found that 8/30 impotent men had slightly raised prolactin levels. Miller et al. (1980) reported no significant differences in prolactin levels between impotent men and controls, and finally Karasek et al. (1981) compared 65 impotent men with 18 controls and found the impotent men to have

mean prolactin levels which were lower than the controls! Obviously with this contradictory evidence, no conclusions can be made at present. However, the editorial comment on the Miller et al. (1980) paper is worthy of discussion, "This carefully done study shows clearly that serum prolactin determinations are not cost effective in the screening of men with erectile dysfunction" (Editorial comment, J. Urol. p.864, 1980). The present author would rather suggest that in cases where patients present with loss of sexual interest, a diagnosis of psychological origin should not be made until an organic cause of the dysfunction, such as hyperprolactinaemia, has been excluded. A routine prolactin determination in such individuals would lead to speedy diagnosis of a sub-group of patients whose sexual dysfunction is secondary to their elevated prolactin level, and which can be readily and effectively treated with bromocriptine.

APPENDIX II

PLASMA STEROIDS AND SEX HORMONE BINDING GLOBULIN ESTIMATION

INTRODUCTION

It is well established that androgen administration to man leads to a reduction in SHBG levels (Anderson, 1974). Administration of Testosterone Undecanoate (T.U.), the new orally effective androgen, leads to (a) a greater proportional elevation of systemic DHT compared with testosterone (Skakkebaek et al., 1981; Franchimont et al., 1978) and (b) a highly significant suppression of SHBG levels (Skakkebaek et al., 1981; Wu et al., 1982*; Sarris et al., 1977). In these studies, and the study described in Chapter 4 of this thesis, the method of SHBG estimation that was used (Anderson et al., 1976) is one where DHT is employed as the ligand, and the amount of exogenous tritiated DHT which becomes bound to the diluted plasma sample reflects the relative SHBG binding capacity of the sample. This assay is based on the principle that SHBG has a higher affinity for binding DHT than other steroids (Anderson, 1974; Mean et al., 1977).

It has been demonstrated that charcoaling of plasma to remove endogenous steroids prior to assay has no effect on the SHBG values derived from normal men (Anderson et al., 1976; Tulchinsky & Chopra, 1973; Rosner, 1972). However, as DHT levels become elevated following T.U. administration it is possible that a proportion of the SHBG will become bound by this circulating DHT, leaving fewer SHBG binding sites to be filled by the tritiated DHT used in the SHBG assay. Therefore, it is hypothesised that the degree of reduction in SHBG levels following T.U. treatment which has recently been reported in the literature may be an overestimation due to this particular method of

*The Wu et al. (1982) paper incorrectly reports the SHBG values by a factor of ten.

SHBG determination.

Materials and Methods

Subjects

Normal male blood samples were collected from sixteen volunteers from hospital staff.

As part of a larger series of investigations into the effects of different androgen preparations and their effects on the endocrinology of the eugonadal man (described in Chapter 4) four normal men (age 19-40 years, man 29.5 years) were recruited from hospital staff.

Design

After a baseline period of one week, each subject was administered T.U. at a dosage of 240mg/day for 21 days, capsules being taken in equal divided doses at 0900, 1300 and 1700 hours. Blood samples were taken at 0900 and 1300 hours on two days per week throughout the four week study period, that is prior to and four hours after the morning dose of T.U.

Hormonal Measurement

The plasma samples were assayed twice to determine SHBG binding; (a) using the standard procedure of Anderson et al. (1976) and (b) after removal of plasma steroids with Dextran Coated Charcoal (DCC) treatment. DHT was measured in each of the men receiving T.U. according to the method of Thorneycroft et al. (1973) after chromatography on celite columns, as described in Chapter 2.

Charcoaling Procedure

To 0.5 mls plasma, 3.5 mls of assay buffer was added containing 12.5 mg Norit A charcoal and 1.25 mg Dextran T70 (Pharmacia). After an

incubation with intermittent mixing for 30 minutes at room temperature, the mixture was centrifuged at 3,000g for 10 minutes. The resultant supernatant was used directly to determine SHBG binding capacity.

Results

T.U. administration (240mg/day for 21 days) resulted in a highly significant increase in plasma DHT levels (pretreatment: 1.61 $\pm$ 0.8 nmol DHT/l (mean $\pm$ S.D.); T.U. treated: 3.77 $\pm$ 2.4 nmol/l; $p < 0.01$, ANOVAR).

Charcoal treatment of plasma from normal men (n=16) did not affect the estimated level of SHBG (untreated: 34.3 $\pm$ 12.3 nmol SHBG/l; DCC treated: 33.6 $\pm$ 12.4 nmol/l; t=0.425, paired t-test, N.S.). In contrast DCC treatment resulted in a highly significant increase in the estimated level of SHBG in plasma samples from men taking T.U. (untreated: 26.7 $\pm$ 5.2 nmol SHBG/l; DCC treated: 30.0 $\pm$ 6.6 nmol/l; t=3.05, paired t-test, $p < 0.01$). This effect of DCC treatment is graphically demonstrated in Fig. II.1.

Discussion

The results confirm previous findings (Anderson et al., 1976; Tulchinsky and Chopra, 1973; Rosner, 1972) that DCC treatment has no effect on the estimation of SHBG in plasma from normal men. However, when samples from men receiving T.U. are assayed, removal of steroids from plasma by DCC treatment has a highly significant effect on the SHBG values obtained, in that DCC treatment produces SHBG values which are significantly higher than those obtained from the same non-charcoal treated samples. This effect is presumably an indirect result of the T.U. treatment which acts to increase circulating DHT levels which

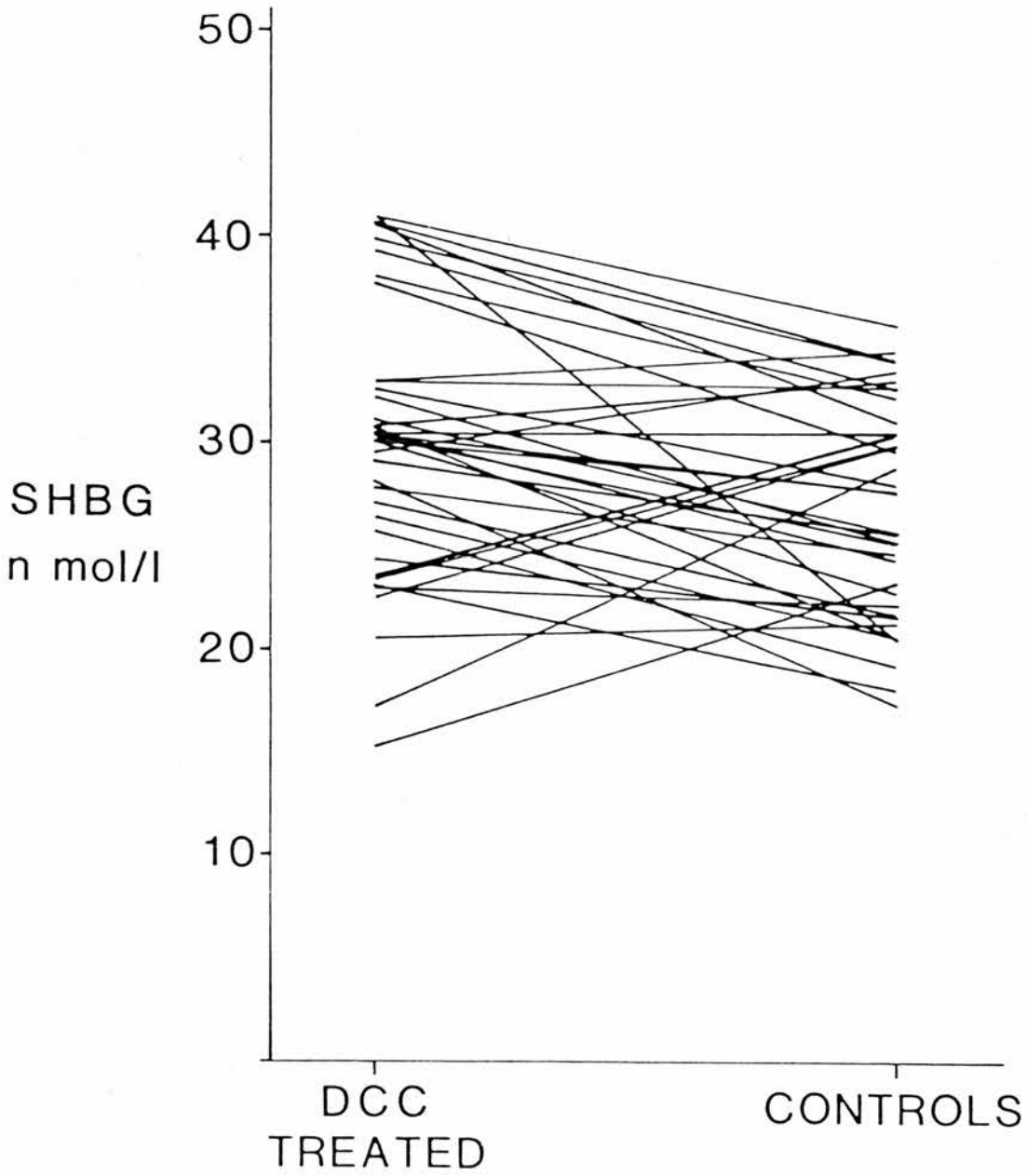


FIGURE II.1

The effect of DCC (charcoal) treatment to remove steroids from plasma samples prior to SHBG estimations using the DHT-ligand binding assay method.

compete with the tritiated assay DHT for binding sites on the protein.

The hypothesis outlined in the introduction suggesting that elevated DHT level, as a result of the T.U. treatment, act to interfere with the accuracy of the SHBG assay has thus been confirmed. It is recommended that samples from men receiving T.U. have steroids removed from plasma samples prior to SHBG estimation when the DHT-binding assay is to be used.

APPENDIX III

AN INVESTIGATION INTO THE RATE OF ABSORPTION OF TESTOSTERONE UNDECANOATE IN THE EUGONADAL MAN

INTRODUCTION

The aim of this small study was to investigate the rate of absorption of testosterone undecanoate (T.U.) in eugonadal men, in light of recent reports in the literature which suggest that individuals may vary in the rate at which plasma testosterone levels peak following T.U. ingestion (Cantrill *et al.* 1983; Schurmeyer *et al.* 1983).

MATERIALS AND METHODS

Three eugonadal male volunteers aged 46 ± 13 yrs. agreed to participate in a study where they were administered T.U. 240 mg/day for three weeks. T.U. absorption curves were carried out twice, (a) after taking their first 80 mg dose of T.U. and (b) again following oral ingestion of 80 mg T.U.; at the end of three weeks treatment with T.U. 240 mg/day. Subjects came into the Edinburgh Royal Infirmary and had blood samples taken every 30 mins. for seven hours, with 80 mg T.U. administered after one hour. Blood samples were assayed for testosterone using the method of Corker & Davidson (1978).

RESULTS

The results of the absorption studies are shown in Figure III.1. Subject A demonstrated a very gradual and slight elevation in circulating testosterone levels which appeared to reach a maximum approximately six hours after ingestion of the T.U. dose. Interestingly, after three weeks of T.U. administration basal testosterone levels were lowered, presumably due to decreased production of endogenous testosterone as a result of the increased negative feedback effect of the exogenous testosterone administration. Subject B showed an absorption peak three hours after T.U. ingestion in

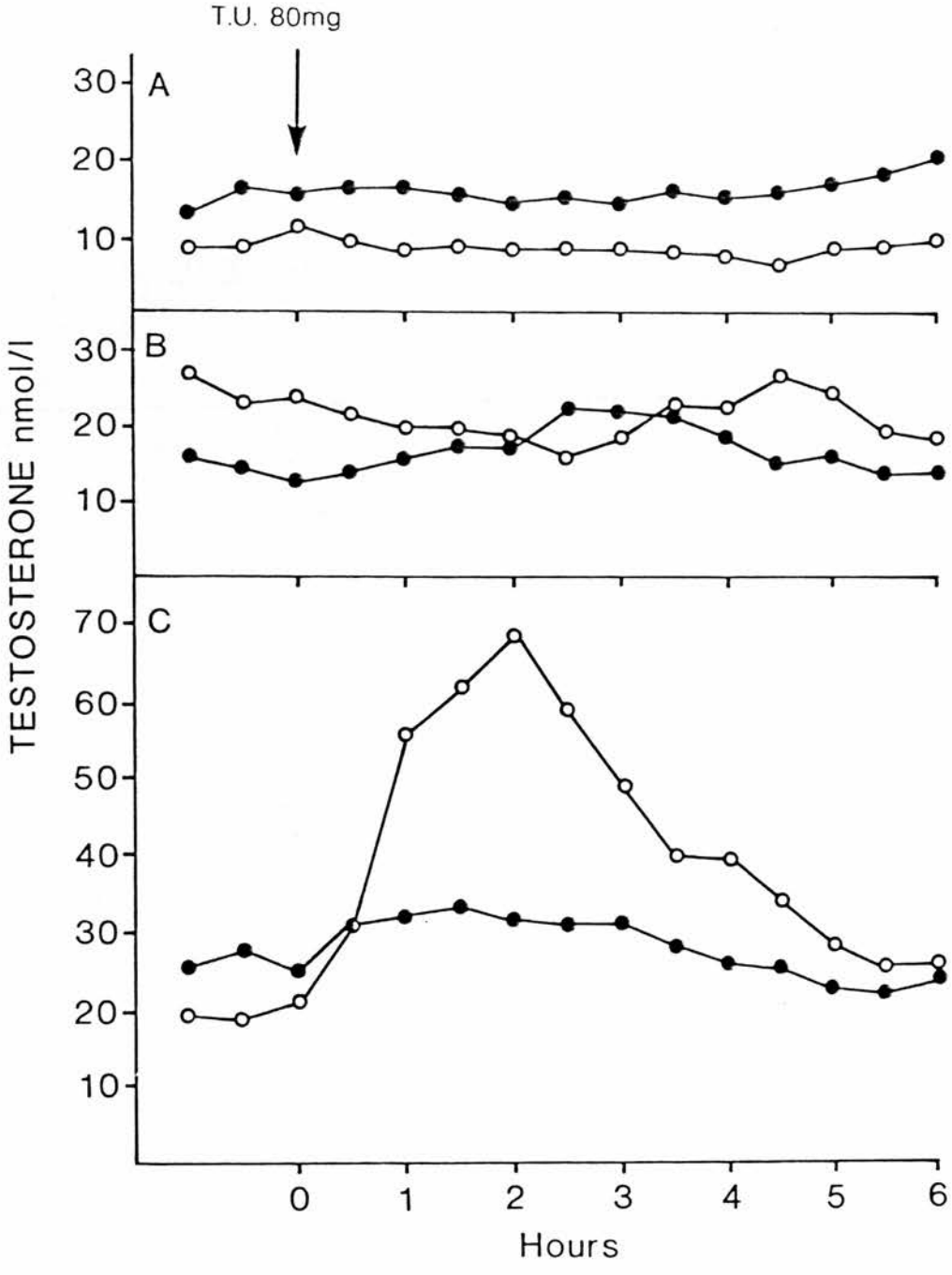


FIGURE III.1

The effect of oral administration of 80 mg T.U. on circulating testosterone levels in 3 eugonadal men:

●—● after their first dose of T.U.

○—○ after three weeks treatment with T.U. 240 mg/day.

the basal condition, but this peak had shifted to four - five hours following three weeks treatment with T.U. 240 mg/day. Subject C demonstrated a very slight increase in circulating testosterone levels one - three hours after the basal T.U. dose, but after three weeks treatment with T.U. 240 mg/day, plasma testosterone levels were massively raised (approximately 70 nmol/l) two hours after oral ingestion of 80 mg T.U.

DISCUSSION

The results of this small study confirm the findings of Cantrill et al. (1983) and Schurmeyer et al. (1983), i.e. that there is a marked degree of inter- and intra-individual variation in T.U. absorption rates. One factor which could possibly contribute to this observed variation is dietary fat content. As T.U. is fat soluble and is absorbed via the lymphatic system, changes in the fat content of the diet could affect the rate of fat absorption and metabolism and hence affect the rate of absorption of T.U.

APPENDIX IV

DAILY ASSESSMENT DIARY QUESTION AND ANSWER FORMS

I Did you awake with an erection this morning? (please tick)

II Mood Scales

Please place a mark on the mood scale lines to indicate how you have felt today. A mark to the extreme left means "not at all" and a mark to the extreme right means "more so than I can ever remember"

1. Cheerful and Happy
2. Fatigued and Tired
3. Sociable and Friendly
4. Energetic
5. Tense and Anxious
6. Irritable
7. Changeable or Up and Down
8. Aggressive
9. Depressed and Unhappy
10. Relaxed

III Sexual Activity

If no sexual activity occurred today, please tick box A. If one of the activities listed below occurred, then enter a number 1-4 in the appropriate box to indicate how satisfactory you found it.

Activity	Rating
M - Masturbation	1 = unsatisfactory or even unpleasant
A.C. - Affectionate intimate contact with partner, i.e. caressing genital areas or breasts	2 = neither satisfactory nor unsatisfactory
S.I. - Sexual Intercourse	3 = quite satisfactory 4 = very satisfactory and pleasant

In the lower box marked E_1, simply insert a tick if you ejaculated on that occasion.

For activities A.C. and S.I., please indicate with a tick whether the activity was self-initiated (s), partner initiated (p) or initiated by both (b)

Sexual Thoughts

IV A. Please indicate how often you have found yourself thinking sexy thoughts today by marking the line A in the appropriate place. A mark to the extreme left means "no sexual thoughts at all" and a mark to the extreme right means "sexual thoughts frequent".

B. If you have had any sexy thoughts today, please indicate how often you have found yourself having feelings of sexual excitement accompanying your thoughts by marking the line B in the appropriate place. A mark to the extreme left means "sexual thoughts not associated with feelings of sexual excitement" and a mark to the extreme right means "sexual thoughts frequently associated with feelings of sexual excitement".

I. YES ☐ NO ☐ DATE .....

II. 1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

7. _____

8. _____

9. _____

10. _____

III. A ☐ A.C. ☐ s ☐ p ☐ b ☐

M ☐ E_1 ☐

E_1 ☐ S.I. ☐

E_1 ☐ s ☐ p ☐ b ☐

IV

A. _____

B. _____

APPENDIX V

STRUCTURED INTERVIEW

1. Frequency of Sexual Activity

"How often have you engaged in sexual intercourse or masturbation in the last x weeks?"

Record frequency.

2. Level of Sexual Interest

"How often during the past x weeks have you found yourself thinking about sex with any interest, appetite or desire. Would you say it was several times a day, a week, once or twice a month, or less?"

0. Thoughts about sex absent, or never associated with desire
1. Rarely (less than once a month)
2. About once a month
3. Less than once a week, more than once a month
4. At least once a week
5. Several times a week
6. At least once a day

3. Negative Feelings During Sexual Contact

"You have made love approximately x times in the last x weeks. On what proportion of these occasions have you felt, at some stage, any unpleasant, or anxious, or tense feelings during lovemaking?"

A. 0. Rarely has sexual contact without anxious feelings
   1. Unpleasant feelings on about 75% of occasions
   2. Unpleasant feelings on about 50% of occasions
   3. Unpleasant feelings on about 25% of occasions
   4. Rarely has unpleasant feelings

B. "How strong are these feelings?"

1. Very mild
2. Mild
3. Moderate
4. Strong
5. Very strong

4. Positive Feelings During Sexual Contact

"What proportion of these occasions did you feel were enjoyable, mainly pleasurable?"

0. No pleasure from sexual contact at any time
1. Experiences pleasure on about 25% of occasions
2. Experiences pleasure on about 50% of occasions
3. Experiences pleasure on about 75% of occasions
4. Rarely fails to experience pleasure

5. Sexual Arousal (non-genital)

"How often during the past x weeks when you have engaged in sexual contact have you found yourself getting generally aroused? By that I mean general excitement, skin or heart rate changes, semi-voluntary body movement, sweating, spontaneous noise, etc.?"

A. Frequency

0. Never
1. Rarely
2. On about 25% of occasions
3. On about 50% of occasions
4. On about 75% of occasions
5. Rarely does not become aroused

B. Strength (show subject rating scale)

0. Calm, no excitement, no general bodily changes

1. Slightly aroused, wanting to continue, little body movement

2. Moderately aroused, feeling excited, less inhibited, moving body during lovemaking, breathing more rapidly

3. Strongly aroused, very excited, making some noises, moving involuntarily, not fully aware of things happening around you

4. Highly aroused, out of control of your body, making loud noises, extremely active bodily movements. Unaware of anything going on around you, close to "passing out"

6. Orgasm

"On what proportion of occasions have you experienced an orgasm during lovemaking?"

A. Frequency

0. Never experiences orgasm in waking state

1. Experiences orgasm on approximately 25% of occasions

2. Experiences orgasm on approximately 50% of occasions

3. Experiences orgasm on approximately 75% of occasions

4. Experiences orgasm on most occasions - rarely not

B. Occasion

0. Never

1. Orgasm in coitus

2. Orgasm during penile stimulation by partner

3. Orgasm during self-stimulation in partner's presence

4. Orgasm during masturbation (alone)

9. Subject does not know if he is orgasmic

7. Erection

"Do you have any difficulty in getting or keeping an erection during lovemaking?"

0. Never has an erection whilst awake

1. Only experiences erection on waking

2. Gets erection, but never during sexual contact with partner

3. Gets erection during loveplay, but insufficient for vaginal intercourse

4. Gets erection sufficient for vaginal intercourse but only when it is not expected to happen

5. Gets erection sufficient for vaginal intercourse on approximately 25% of occasions

6. Gets erection sufficient for vaginal intercourse on approximately 50% of occasions

7. Gets erection sufficient for vaginal intercourse an approximately 75% of occasions.

8. Rarely unable to have vaginal intercourse

8. Ejaculation - Retarded

"Have there been any occasions when you have been unable to ejaculate, or it has taken too long to do so?"

0. Ejaculation or emission never occurs

1. Ejaculation or emission only occurs during sleep

2. Ejaculation occurs when awake but not in partner's presence

3. Ejaculation occurs during sexual contact, but not vaginal intercourse, with difficulty

4. Ejaculation occurs during sexual contact, but not vaginal intercourse, easily

5. Ejaculation occurs during vaginal intercourse on approximately 25% of occasions

6. Ejaculation occurs during vaginal intercourse on approximately 50% of occasions

7. Ejaculation occurs during vaginal intercourse on most occasions

9. Premature Ejaculation

"During intercourse, are you able to control your ejaculation as you would like to?"

0. Always ejaculates before or at time of vaginal entry

1. Nearly always ejaculates within 30 seconds of vaginal entry

2. Can usually delay ejaculation beyond 30 seconds, but not adequate control

3. Occasionally has adequate control

4. Adequate control on about 25% of occasions

5. Adequate control on about 50% of occasions

6. Adequate control on about 75% of occasions

7. Rarely fails to have adequate control

8. Can be delayed but partner urges rapid conclusion

10. Receptivity

"During the past x weeks, on the occasions that your partner has initiated sexual contact, how have you responded?"

0. Partner never initiated sexual contact

1. Nearly always refused to continue

2. Responded with a desire to continue on about 25% of occasions

3. Responded with a desire to continue on about 50% of occasions

4. Responded with a desire to continue on about 75% of occasions

5. Nearly always responsed with a desire to continue

APPENDIX VI

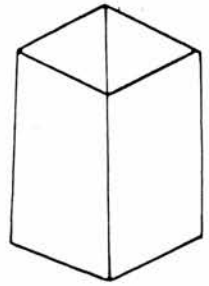
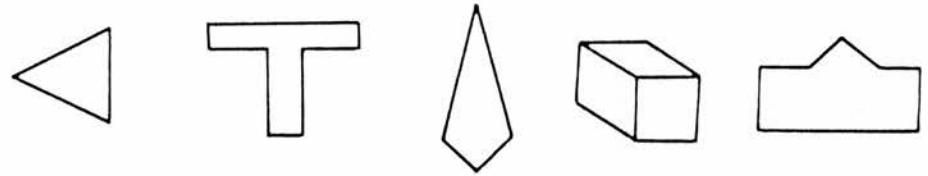
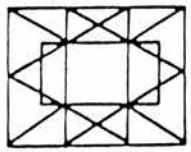
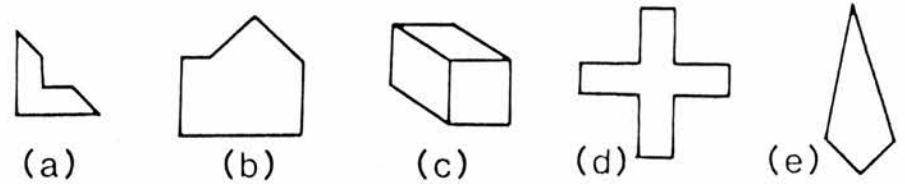
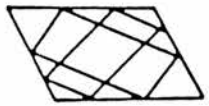
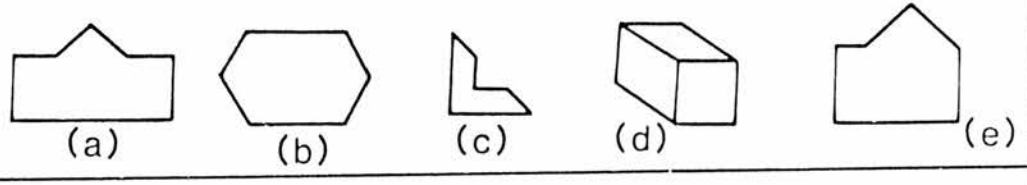
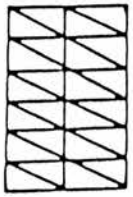
MORRISON'S (1976) MODIFICATION OF THE EMBEDDED FIGURES TEST

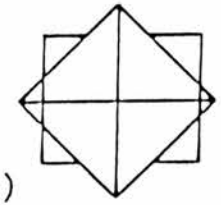
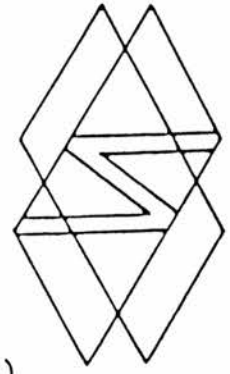
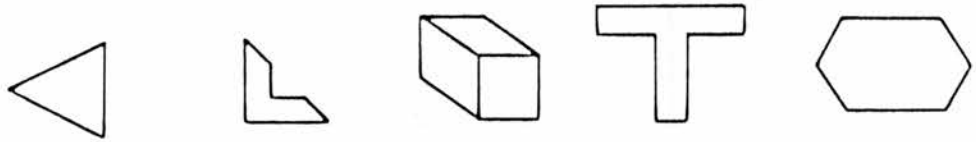
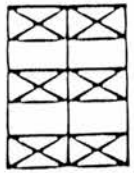
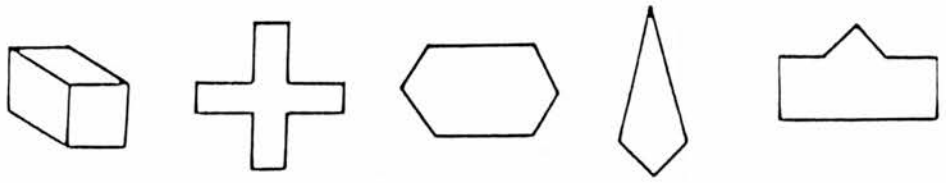
EMBEDDED FIGURES TEST

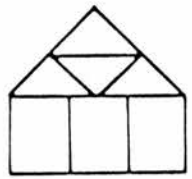
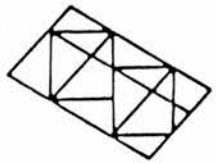
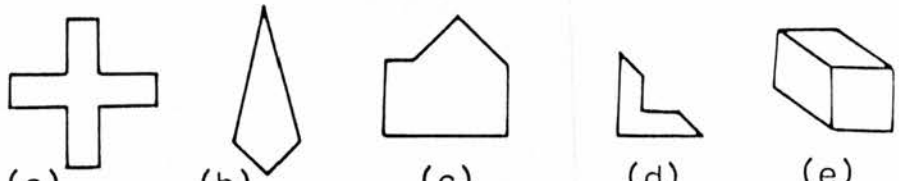
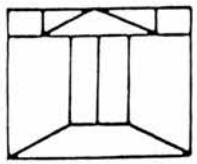
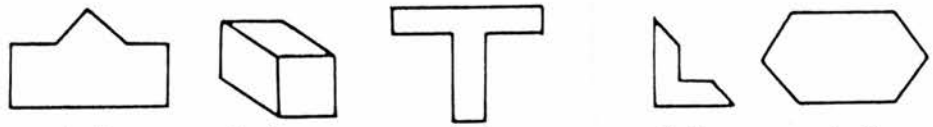
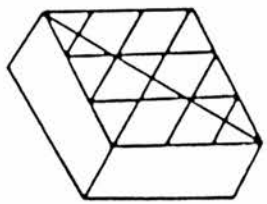
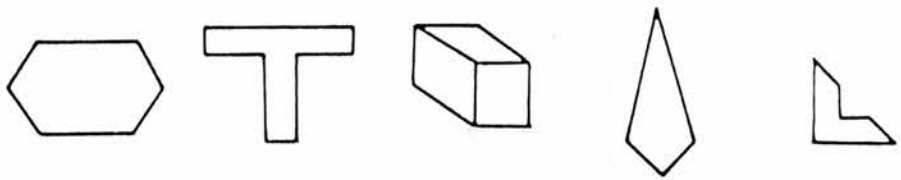
INSTRUCTIONS

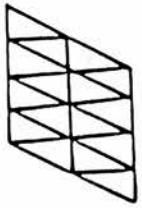
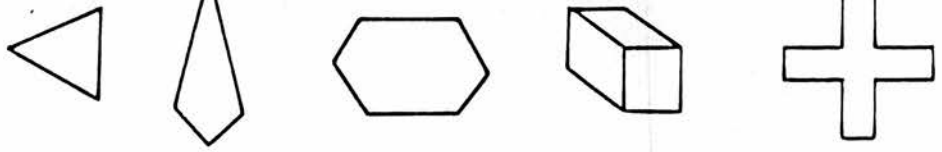
On the following pages are 12 problems. Each problem consists of a complex design (on the left-hand side of the page) and 5 simple shapes. One of these shapes is hidden or obtained within the complex design. Pick out the simple shape and write down its letter in the answer column. Do the same for all of the problems.

You are allowed ten minutes to complete this test

COMPLEX DESIGN	SIMPLE SHAPES	ANSWERS
1) 	 (a) (b) (c) (d) (e)	
2) 	 (a) (b) (c) (d) (e)	
3) 	 (a) (b) (c) (d) (e)	
4) 	 (a) (b) (c) (d) (e)	

COMPLEX DESIGN	SIMPLE SHAPES	ANSWERS
5) 	 (a) (b) (c) (d) (e)	
6) 	 (a) (b) (c) (d) (e)	
7) 	 (a) (b) (c) (d) (e)	

COMPLEX DESIGN	SIMPLE SHAPES	ANSWERS
8) 	 (a) (b) (c) (d) (e)	
9) 	 (a) (b) (c) (d) (e)	
10) 	 (a) (b) (c) (d) (e)	
11) 	 (a) (b) (c) (d) (e)	

COMPLEX DESIGN	SIMPLE SHAPES	ANSWERS
 12)	 (a) (b) (c) (d) (e)	